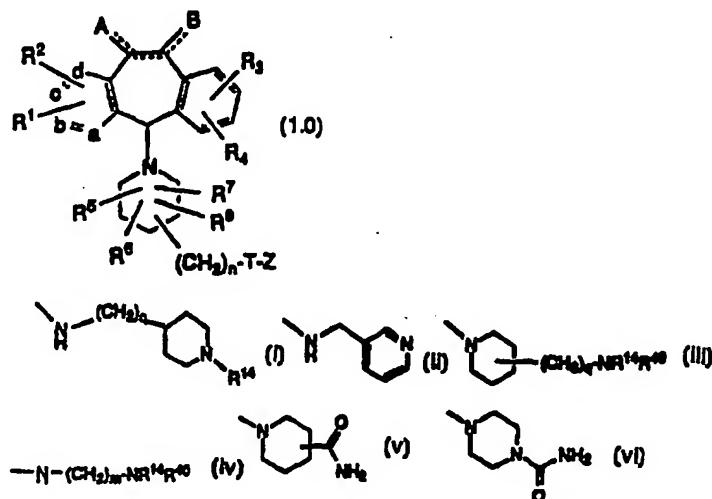




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(54) Title: NOVEL TRICYCLIC PIPERIDINYL COMPOUNDS USEFUL AS INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE



(57) Abstract

Novel tricyclic compounds of formula (1.0) or a pharmaceutically acceptable salt or solvate thereof, wherein: one of a, b, c, and d represents N or NR⁹, wherein R⁹ is O-, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or each of a, b, c and d is independently selected from CR¹ or CR²; each R¹ and each R² is independently selected from H, halo, -CR₃, -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)R¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NHSO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹, -SR¹¹N(R⁷⁵)²; n is 0 (zero), 1, 2, 3, 4, 5 or 6; T is -CO-; -SO-; -SO₂-; or -CR³⁰R³¹-; Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, -OR⁴⁰, -SR⁴⁰, -CR⁴⁰R⁴², -NR⁴⁰R⁴², formulae (i), (ii), (iii), (iv), (v) and (vi). Pharmaceutical compositions are disclosed which are inhibitors of the enzyme, farnesyl protein transferase. Also disclosed is a method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells. The method comprises administering the novel tricyclic compound to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human.

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NOVEL TRICYCLIC PIPERIDINYL COMPOUNDS USEFUL AS INHIBITORS
OF FARNESYL-PROTEIN TRANSFERASE

5

BACKGROUND

Patent application WO 95/00497 published 5 January 1995 under the Patent Cooperation Treaty (PCT) describes compounds which inhibit the enzyme, farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of Ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., *Science*, Vol. 260, 1834 to 1837, 1993).

In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be additional compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

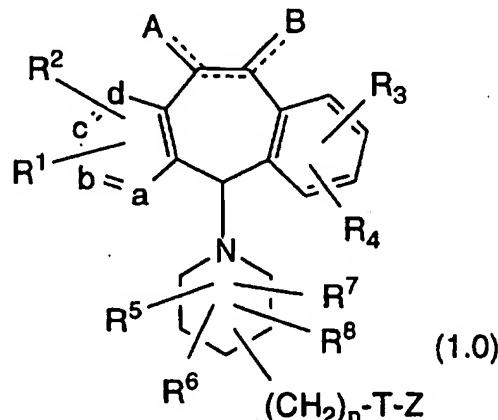
30 SUMMARY OF THE INVENTION

Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, *in vitro*; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell

growth in culture induced by transforming Ras. Several compounds of this invention have been demonstrated to have anti-tumor activity in animal models.

This invention provides a method for inhibiting the abnormal growth of 5 cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated 10 as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

Compounds useful in the claimed methods are represented by Formula 1.0:



15 or a pharmaceutically acceptable salt or solvate thereof, wherein:

one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or

20 each of a, b, c, and d are independently selected from CR¹ or CR²; each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰, -COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹, -NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NHSO₂R¹⁰, -CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹, -SR¹¹N(R⁷⁵)₂ wherein each R⁷⁵ is independently selected from H and -C(O)OR¹¹, benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, -OR¹⁰ or -CO₂R¹⁰;

25 R³ and R⁴ are the same or different and each independently represents H, any of the substituents of R¹ and R², or R³ and R⁴ taken

together represent a saturated or unsaturated C₅-C₇ fused ring to the benzene ring (Ring III);

5 R⁵, R⁶, R⁷ and R⁸ each independently represents H, -CF₃, -COR¹⁰, alkyl or aryl, said alkyl or aryl optionally being substituted with -OR¹⁰, -SR¹⁰, -S(O)R¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂, -NO₂, -COR¹⁰, -OCOR¹⁰, -OCO₂R¹¹, -CO₂R¹⁰, OPO₃R¹⁰, or R⁵ is combined with R⁶ to represent =O or =S and/or R⁷ is combined with R⁸ to represent =O or =S;

R¹⁰ represents H, alkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, aryl, aralkyl or -NR⁴⁰R⁴² wherein R⁴⁰ and R⁴² independently represent H, aryl,

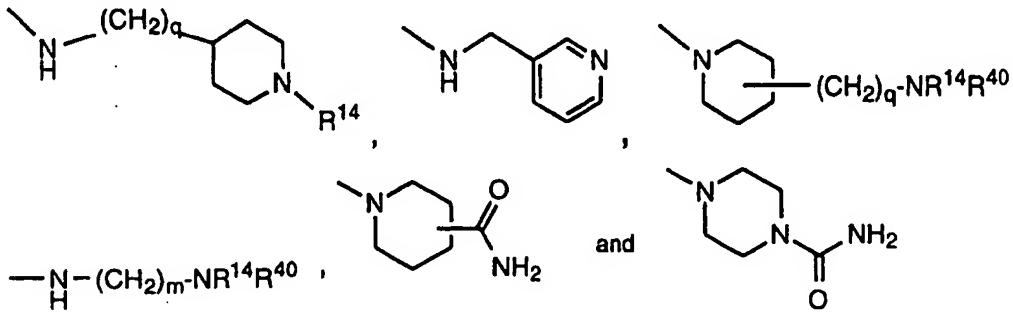
10 alkyl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl and alkynyl;

R¹¹ represents alkyl or aryl;

the dotted line between carbon atoms 5 and 6 represents an optional 15 double bond, such that when a double bond is present, A and B independently represent -NO₂, -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or -OC(O)R¹⁰, and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H₂, -(OR¹¹)₂, H and halo, dihalo, alkyl and H, (alkyl)₂, -H and -OC(O)R¹⁰, H and -OR¹⁰, oxy, aryl and H, =NOR¹⁰ or -O- 20 (CH₂)_p-O- wherein p is 2, 3 or 4;

n is 0 (zero), 1, 2, 3, 4, 5 or 6;

25 T is -CO-; -SO-; -SO₂-; or -CR³⁰R³¹- wherein R³⁰ and R³¹ independently represent H, alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; and Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, -OR⁴⁰, -SR⁴⁰, -CR⁴⁰R⁴², -NR⁴⁰R⁴²,



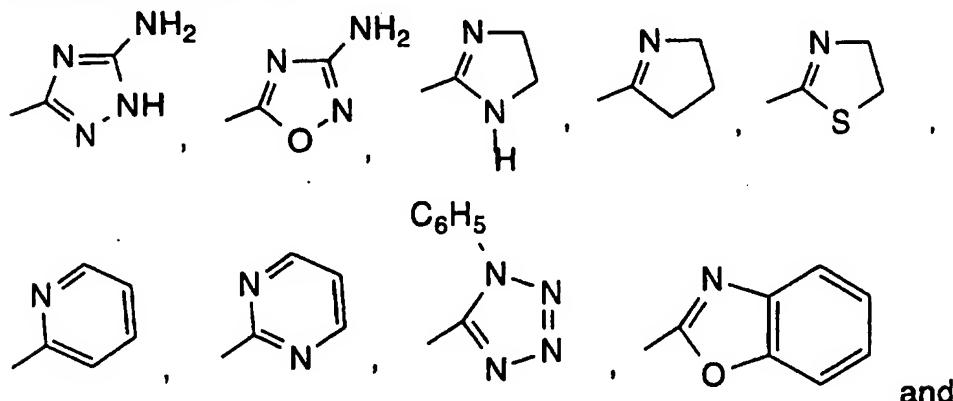
wherein n, R⁴⁰ and R⁴² are defined hereinbefore,

30 m is 2, 3, 4, 5, 6, 7 or 8;

q is 0 (zero), 1 or 2;

and R¹⁴ represents H, C₁₋₆ alkyl, aralkyl, heteroaryl, acyl, carboxamido, carboxamidoalkyl, cyano, alkoxy carbonyl, aralkyloxycarbonyl, D- and

L-amino acids covalently bonded through the carboxyl group, imido, imidamido, sulfamoyl, sulfonyl, dialkylphosphinyl, N-glycosyl,



and

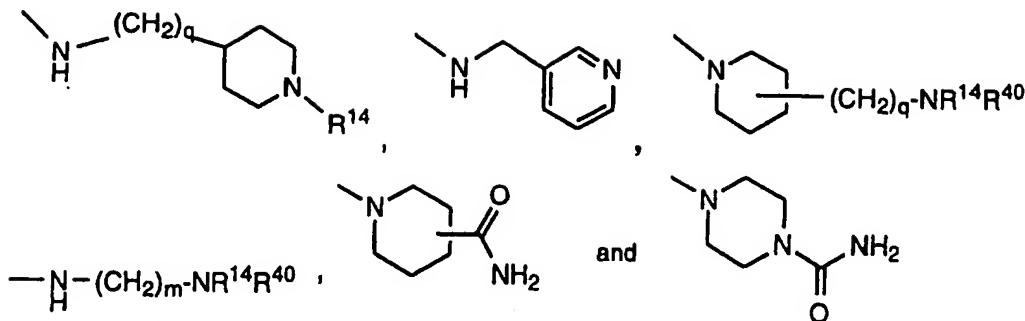
5 -C(NHCH₃)=CHNO₂,
with the proviso that when T is -SO-, Z is not -NR⁴⁰R⁴².

In the compounds of formula (1.0), preferably a is N; b, c and d are carbon; A and B each represent H₂ and the optional double bond is absent.

10 Also preferred is that R¹ and R⁴ are H and R² and R³ are halo selected from chloro and bromo; or R¹ is H and R², R³ and R⁴ are halo selected from chloro and bromo. Also preferred is that R² and R³ are halo in the 3- and the 8-position on the ring structure; or R², R³ and R⁴ are in the 3-, 8- and 10-position on the ring structure. Also preferred is that R² is Br and R³ is Cl in the 3- and the 8-position on the ring structure; or R² is Br, R³ is Cl and R⁴ is Br in the 3-, 8- and 10- position on the ring structure. Also preferred is that each of R⁵, R⁶, R⁷ and R⁸ is H. Also preferred is that the moiety -(CH₂)_n-T-Z is bonded at the 2-, 3- or 4-position on the piperdinyl ring, more preferably at the 2- or 3-position on the piperdinyl ring.

20 Also preferred in the compounds of formula (1.0) is that n is zero, 1 or 2; T is -CO- and Z is -NR⁴⁰R⁴² wherein R⁴⁰ and R⁴² independently represent H, aryl, alkyl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroalkyl, cycloalkyl or cycloalkylalkyl; or

25 Z is



wherein R^{40} is defined hereinbefore,

m is 2, 3 or 4;

- 5 q is 0 (zero), 1 or 2;
- and R^{14} represents H, C₁₋₆ alkyl, aralkyl, heteroaryl, acyl, carboxamido, carboxamidoalkyl, cyano, alkoxy carbonyl, aralkyloxycarbonyl imido, imidamido, sulfamoyl, sulfonyl, dialkylphosphinyl, N-glycosyl or C(NHCH₃)=CHNO₂. More preferably, n is zero; Z is -NR⁴⁰R⁴² wherein R⁴⁰ represents H and R⁴²
- 10 represents heteroarylalkyl. More preferably R⁴⁰ is H and R⁴² is the heteroaryl moiety 3-pyridylmethyl.

In another embodiment, the present invention is directed toward a pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound (1.0) in combination with a pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed toward a method for inhibiting the abnormal growth of cells, including transformed cells, comprising administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs, and (4) benign or malignant cells that are activated by mechanisms other than the Ras protein. Without wishing to be bound by theory, it is believed that these compounds may function either through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer, or through inhibition of ras farnesyl protein transferase, thus making them useful for their antiproliferative activity against ras transformed cells.

The cells to be inhibited can be tumor cells expressing an activated ras oncogene. For example, the types of cells that may be inhibited include pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

5 Also, the inhibition of the abnormal growth of cells by the treatment with compound (1.0) may be by inhibiting ras farnesyl protein transferase. The inhibition may be of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene. Alternatively,

10 compounds (1.0) may inhibit tumor cells activated by a protein other than the Ras protein.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of compound (1.0) to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a

15 method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma),

20 colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting

25 proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an effective amount of the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein, to

30 a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the carbonyl piperazinyl and piperidinyl compounds (1.0) described herein.

35 In another embodiment, the present invention is directed toward a method for inhibiting ras farnesyl protein transferase and the farnesylation of the oncogene protein Ras by administering an effective amount of compound (1.0) to mammals, especially humans. The administration of the compounds

of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

DETAILED DESCRIPTION OF THE INVENTION

The following solvents and reagents are referred to herein by the

5 abbreviations indicated:

- 10 tetrahydrofuran (THF);
- ethanol (EtOH);
- methanol (MeOH);
- ethyl acetate (EtOAc);
- 15 N,N-dimethylformamide (DMF);
- trifluoroacetic acid (TFA);
- 1-hydroxybenzotriazole (HOBT);
- 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC);
- dimethylsulfoxide (DMSO);
- 15 4-methylmorpholine (NMM);
- dimethylaminopyridine (DMAP); and
- dimethoxyethane (DME).
- 20 t-butoxycarbonyl (BOC)
- acetyl(OAc)

20

As used herein, the following terms are used as defined below unless otherwise indicated:



or - indicates a pure isomer;

- when attached to a carbon atom labeled with an asterisk (*),

25 indicates a separated isomer whose stereochemistry is not established;

- indicates a racemic mixture;

M⁺ -represents the molecular ion of the molecule in the mass spectrum;

30 MH⁺ -represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

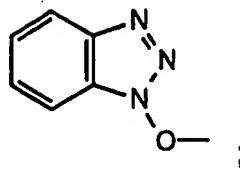
Bu-represents butyl;

Et-represents ethyl;

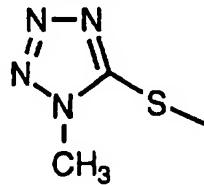
Me-represents methyl;

Ph-represents phenyl;

35 benzotriazol-1-yloxy represents



1-methyl-tetrazol-5-ylthio represents



acyl-a moiety of the formula -COR¹⁵ wherein R¹⁵ represents H,

5 C₁-6alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl or -(CH₂)_kNR⁸⁰R⁸¹ wherein k is 1 or 2, and R⁸⁰ and R⁸¹ may independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, aryl or aralkyl;

10 alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms (i.e. C₁-6 alkyl); for example methyl, ethyl, propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; wherein said alkyl and said C₁-6 alkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino (-NH₂), alkylamino, cyano (-CN), -CF₃, dialkylamino, hydroxy, oxy (=O), phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -NCOR¹⁰ or -COOR¹⁰.

15 alkoxy-an alkyl moiety of one to 20 carbon atoms covalently bonded to an adjacent structural element through an oxygen atom, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like; wherein said alkoxy group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

20 alkoxycarbonyl - represents a alkoxy moiety, as defined above, covalently bonded to a carbonyl moiety (-CO-) through an oxygen atom, for example, -COOCH₃, -COOCH₂CH₃ and -COOC(CH₃)₃;

25 alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6

carbon atoms; wherein said alkenyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰,

5 -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms; wherein said alkynyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

10 amino acid- refers to organic compounds having both an amino group (-NH₂) and a carboxyl group (-COOH). Representative amino acids include glycine, serine, alanine, phenylalanine, tyrosine, S-methyl methionine and histidine;

15 aryl (including the aryl portion of aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is phenyl), wherein said aryl group optionally can be fused with aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings; and wherein any of the 20 available substitutable carbon and nitrogen atoms in said aryl group and/or said fused ring(s) may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

25 aralkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or 30 more aryl groups; wherein said aralkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

35 Representative aralkyl groups include benzyl and diphenylmethyl;

aralkyloxy - represents an aralkyl group, as defined above, covalently bonded to an adjacent structural element through an oxygen atom, for example, phenylmethyloxy and phenylethyoxy;

aralkyloxycarbonyl - represents an aralkyloxy group, as defined above, covalently bonded to a carbonyl moiety (-CO-) through an oxygen atom, for example, -COOCH₂C₆H₅ and -COOCH₂CH₂C₆H₅;

5 carboxamido - represents a moiety of the formula -CONR⁴⁰R⁴², including -CONH₂;

carboxamidoalkyl - represents an alkyl group, as defined above, wherein a hydrogen atom of the alkyl moiety has been substituted with a carboxamido moiety, as defined above, through the carbonyl (-CO) portion of the carboxamido moiety, for example, -CH₂CONH₂ and -CH₂CH₂CONH₂;

10 cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms; wherein said cycloalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, 15 -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

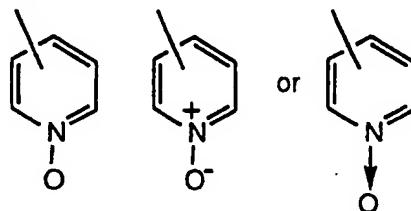
20 cycloalkylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms of the alkyl moiety have been substituted with one or more cycloalkyl groups; wherein said cycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

25 halo-represents fluoro, chloro, bromo and iodo;

heteroalkyl-represents straight and branched carbon chains containing from one to twenty carbon atoms, preferably one to six carbon atoms interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N-; wherein any of the available substitutable carbon and nitrogen atoms in said 30 heteroalkyl chain may be optionally and independently substituted with one, two, three or more of the following: halo, C₁-C₆ alkyl, aryl, cyano, hydroxy, alkoxy, oxy, phenoxy, -CF₃, -OCF₃, amino, alkylamino, dialkylamino, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, or -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

35 heteroaryl-represents cyclic groups having at least one heteroatom selected from O, S and N, said heteroatom(s) interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups containing from 2 to

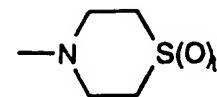
14 carbon atoms, wherein said heteroaryl group optionally can be fused with one or more aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings; and wherein any of the available substitutable carbon or nitrogen atoms in said heteroaryl group and/or said fused ring(s) may be optionally and independently substituted with one, two, three or more of the following: halo, C₁-C₆ alkyl, aryl, cyano, hydroxy, alkoxy, oxy, phenoxy, -CF₃, -OCF₃, amino, alkylamino, dialkylamino, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, or -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰. Representative heteroaryl groups can include, for example, furanyl, imidazoyl, pyrimidinyl, triazolyl, 2-, 3- or 4-pyridyl or 2-, 3- or 4-pyridyl N-oxide wherein pyridyl N-oxide can be represented as:



heteroarylalkyl - represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heteroaryl groups; wherein said heteroarylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰; as exemplified by 2-, 3- or 4-pyridylmethyl or 2-, 3- or 4-pyridylmethyl N-oxide;

heterocycloalkyl-represents a saturated, branched or unbranched carbocyclic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 heteroatoms selected from -O-, -S- and -N-, wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein any of the available substitutable carbon and nitrogen atoms in the ring may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰

Representative heterocycloalkyl groups can include morpholinyl, 2- or 3-tetrahydrofuryl, 2- or 3-tetrahydrothienyl, 1-, 2-, 3- or 4-piperidinyl, 2- or 3-

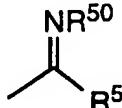


wherein

pyrrolidinyl, 1-, 2- or 3-piperazinyl, 2- or 4-dioxanyl, or t is 0, 1 or 2;

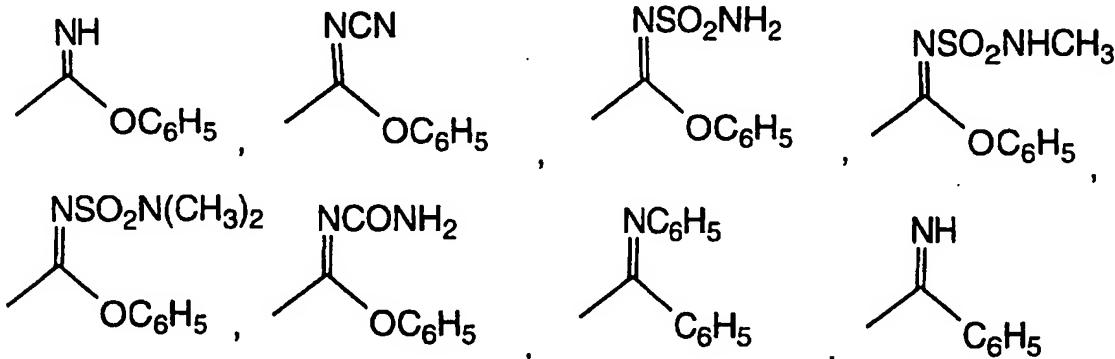
5 heterocycloalkylalkyl- represents an alkyl group, as defined above, wherein one or more hydrogen atoms have been replaced by one or more heterocycloalkyl groups; wherein optionally, said ring may contain one or two unsaturated bonds which do not impart aromatic character to the ring; and wherein said heterocycloalkylalkyl group may be optionally and independently substituted with one, two, three or more of the following: halo, alkyl, aryl, alkoxy, amino, alkylamino, cyano, -CF₃, dialkylamino, hydroxy, oxy, 10 phenoxy, -OCF₃, heterocycloalkyl, -SO₂NH₂, -NHSO₂R¹⁰, -SO₂NHR¹⁰, -SO₂R¹⁰, -SOR¹⁰, -SR¹⁰, -NHSO₂, -NO₂, -CONR¹⁰, -NCOR¹⁰ or -COOR¹⁰;

15 imido - represents a moiety of the formula

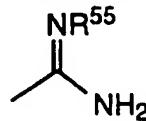


wherein and R⁵⁰ represents H, cyano, aryl, -SO₂NH₂, -SO₂NR⁴⁰R⁴² and carboxamido and R⁵¹ represents aryl and aryloxy.

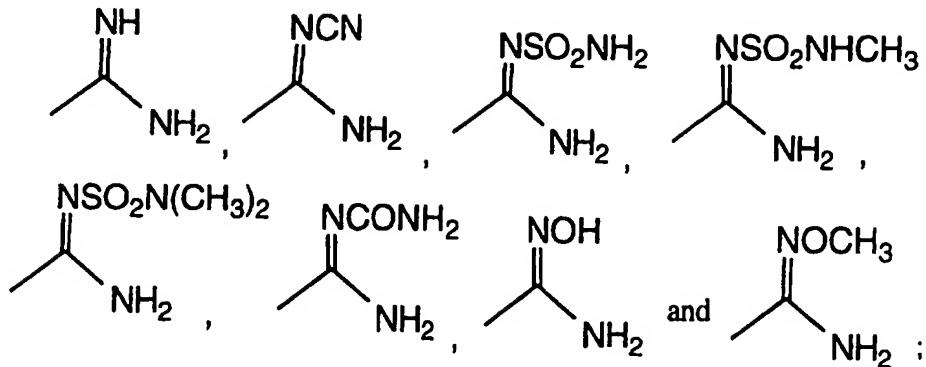
15 Representative imido groups can include, for example,



imidamido - represents a moiety of the formula

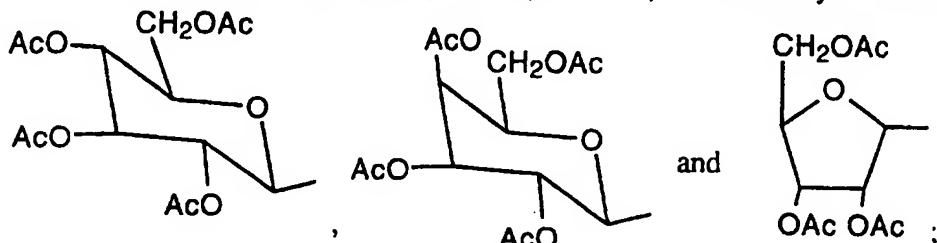


20 wherein and R⁵⁵ represents H, cyano, -SO₂NH₂, -SO₂NR⁴⁰R⁴², carboxamido, hydroxy and alkoxy. Representative imidamido groups can include, for example,



N-glycosyl- represents a pyranosyl or furanosyl monosaccharide.

Representative N-glycosyl groups include (N → 1)-tetra-O-acetyl-D-glucosyl, (N → 1)-tetra-O-acetyl-D-galactosyl and (N → 1)-tri-O-acetyl-D-ribosyl, e.g.



5

D-glycosyl

D-galactosyl

D-ribosyl

1-amino-2-nitroethyl represents the formula: $-\text{C}(\text{NHCH}_3)=\text{CHNO}_2$;

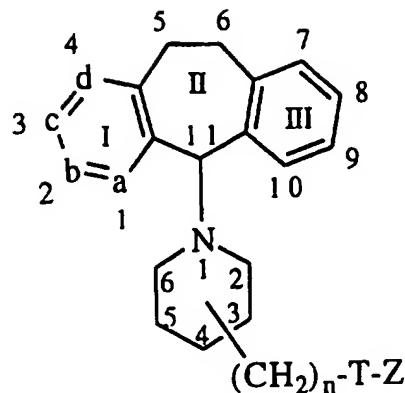
dialkylphosphinyl - represents a phosphine (-PO) moiety covalently bonded to two alkyl groups. A representative dialkylphosphinyl group is $-\text{PO}(\text{CH}_3)_2$.

10 sulfamoyl - represents a moiety of the formula $-\text{SO}_2\text{R}^{60}$ wherein R^{60} represents amino, alkylamino and dialkylamino. Representative sulfamoyl groups can include, for example, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{NHCH}_3$, $-\text{SO}_2\text{N}(\text{CH}_3)_2$.

sulfonyl - represents a moiety of the formula $-\text{SO}_2\text{R}^{60}$ wherein R^{60} represents alkyl, aryl and arylalkyl. Representative sulfonyl groups can

15 include, for example, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{C}_6\text{H}_5$, $-\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3$, and $-\text{SO}_2\text{CH}_2\text{C}_6\text{H}_5$.

Reference to the position of the substituents R^1 , R^2 , R^3 , and R^4 is based on the numbered ring structure:



Certain compounds of the invention may exist in different stereoisomeric forms (e.g., isomers such as enantiomers and diastereoisomers). The invention contemplates all such stereoisomers both in pure form and in mixture, including racemic mixtures. For example, the carbon atom at the C-11 position can be in the S or R stereoconfiguration. Also, the carbon atom at the C-2, C-3, C-5 and C-6 positions of the piperidinyl moiety bonded at C-11 can also be in the S or R stereoconfiguration.

5

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-15 methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

20

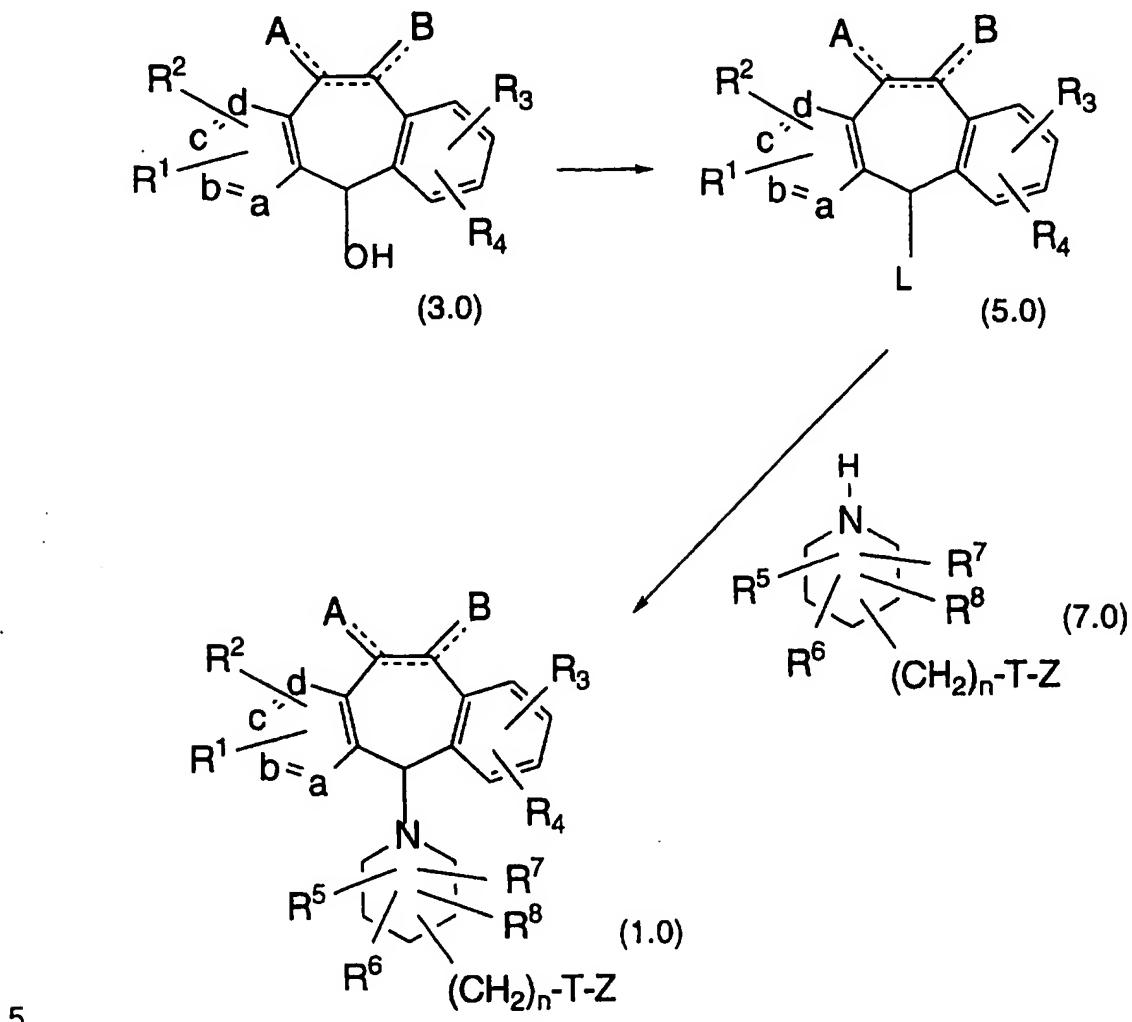
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30

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of the present invention can be prepared according to the following Scheme I:

Scheme 1



5

wherein L represents a leaving group such as halo, preferably chloro or a leaving group such as o-tosyl and o-mesyl; the dotted line represents a single or double bond; and a, b, c, d, A, B, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, n, T and Z are as defined hereinbefore.

10 Referring to the Scheme I, compounds of formula (5.0) can be prepared by reacting the compounds of formula (3.0) with a halogenating agent or a sulfonylating agent in the presence of a suitable base, and optional aprotic solvent, in amounts and under conditions effective to give compounds (5.0). Suitable bases include organic bases such as pyridine and triethylamine; or

15 inorganic bases of alkali and alkaline earth metals including carbonates such as sodium, lithium, potassium and cesium carbonates, hydroxides such as sodium, lithium and potassium hydroxides; hydrides such as sodium or

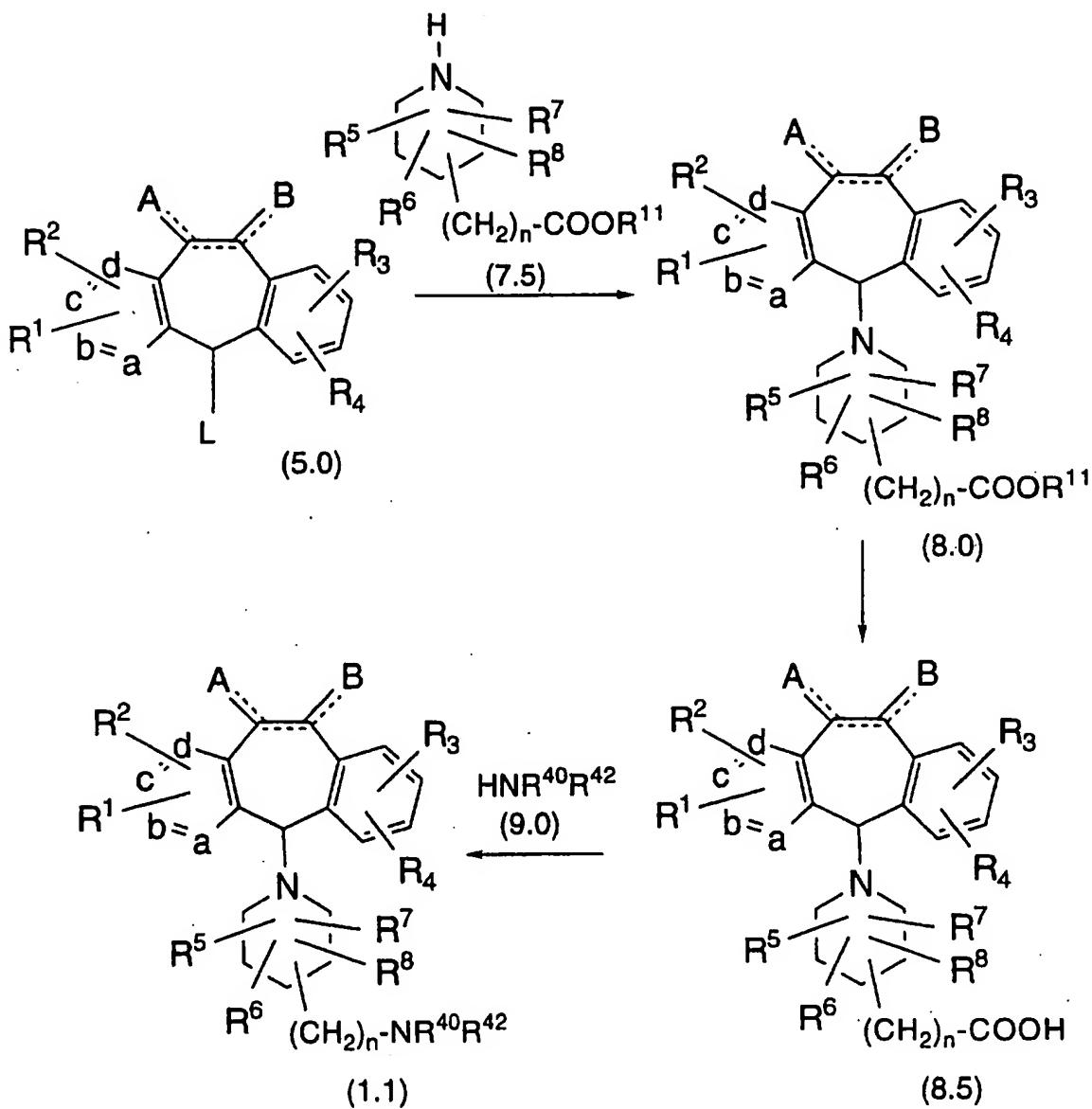
potassium hydride; and sodium t-butoxide, preferably sodium hydride. Suitable aprotic solvents include ethers, DMF, DMSO, THF, DME and mixtures thereof, preferably DMF. Preferably the halogenating agent is a chlorinating agent, such as thionyl chloride. The sulfonylating can be 5 methane sulfonyl chloride or toluene sulfonyl chloride. The amounts of the halogenating agent or the sulfonylating agent can range from about one to about 10 moles per mole of compound (3.0). Temperatures can range from 0° to 50°C, or reflux of the reaction mixture.

The desired tricyclic piperidinyl compounds of formula (1.0) can be 10 prepared by reacting the compounds of formula (5.0) with a suitably substituted piperidinyl compound of formula (7.0) in the presence of a suitable base and optional aprotic solvent, such as those described above, to give compounds (1.0). The amounts of the substituted piperidinyl compound of formula (7.0) to compound (5.0) can range from about one to about 10 moles 15 per mole of compound (5.0). Temperatures can range from about room temperature to about 80°C.

The tricyclic piperidinyl compounds of formula (1.0) can be isolated from the reaction mixture using conventional procedures, such as, for example, extraction of the reaction mixture from water with organic solvents, 20 evaporation of the organic solvents, followed by chromatography on silica gel or other suitable chromatographic media.

Selected compounds of formula (1.0) can be prepared in accordance with Scheme 2.

Scheme 2



wherein L represents a leaving group, preferably chloro; the dotted line represents a single or double bond; and a, b, c, d, A, B, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹¹, R⁴⁰, R⁴² and n are as defined hereinbefore.

5 Referring to the Scheme 2, compounds of formula (8.0) can be
prepared by reacting the compounds of formula (5.0) with a piperidinyl
carboxylic acid ester of formula (7.5) in the presence of a base and optional
aprotic solvent, in amounts and under conditions effective to give compounds
(8.0). Suitable bases and aprotic solvents are described hereinbefore. The
10 amounts of piperidinyl compound (7.5) can range from about 1 to about 10
moles per mole of compound (5.0). Temperatures can range from room

temperature to about 80°C. Compound (8.0) can be isolated as described hereinbefore.

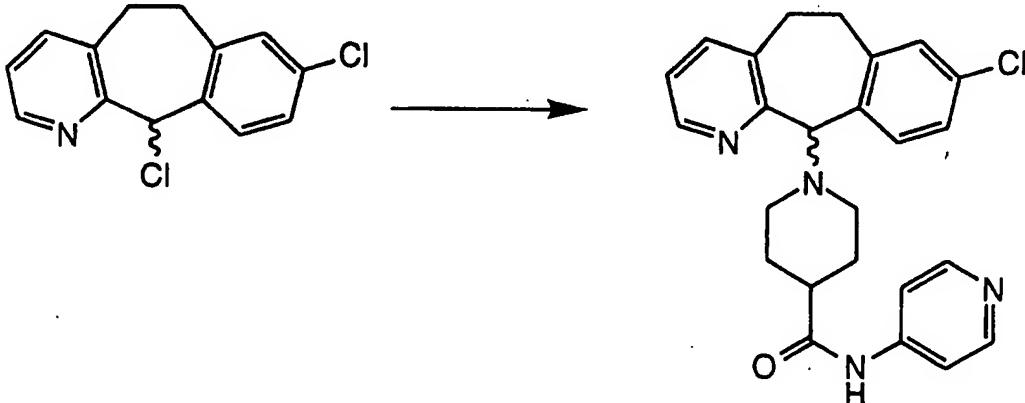
Carboxylic acid compounds of formula (8.5) can be prepared by hydrolyzing carboxylic acid ester (8.0) with an excess amount of acid or base.

5 Suitable acids include inorganic acids, organic acids or a mixture thereof. Inorganic acids include hydrogen chloride, hydrogen bromide, sulfuric acid, nitric acid, phosphoric acid, perchloric acid and the like. Organic acids include acetic, citric, formic, maleic, tartaric, methanesulfonic acid and arylsulfonic acids. Suitable bases, such as sodium hydroxide or lithium 10 hydroxide, preferably in an aqueous alcohol, have been described hereinbefore. The temperature can range from about 0°C to about 100°C.

The desired amide compounds of formula (1.1) can be prepared by reacting the compounds of formula (8.5) with a suitable amine of formula (9.0) in the presence of a coupling agent such as DEC/HOBt, a base such as NMM 15 and a suitable aprotic solvent effective to give amide compound (1.1). Suitable bases and aprotic solvents are described hereinbefore. The amounts of amine (9.0) can range from about 1 to about 10 moles per mole of carboxylic acid (8.5). Temperatures can range from 0° to 100°C. Compound (1.1) can be isolated as described hereinbefore.

20 Compounds of the present invention and preparative starting materials therof, are exemplified by the following examples, which should not be construed as limiting the scope of the disclosure.

EXAMPLE 1. 1-[8-Chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] 25 pyridin-11-yl]-N-(4-pyridinyl)-4-piperidinecarboxamide



8,11-Dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridine (prepared as described in Preparative Example 7, Step B in INO291K) (0.088g; 1 equivalent) in anhydrous toluene (0.819 ml) is added to anhydrous 30 DMSO (1.5ml). 4-Piperidinyl-N-(4-pyridinyl)carboxamide (0.0684g; 1

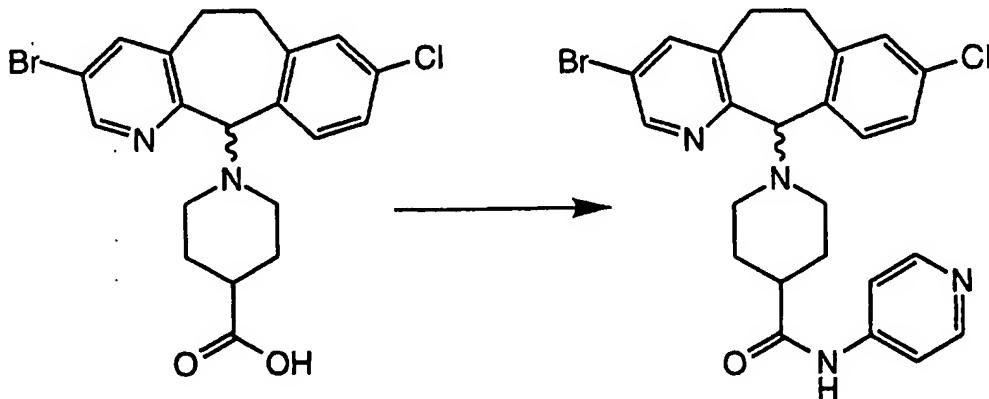
equivalent) (prepared as described in Preparative Example 1, Step C below) is added and the mixture is stirred at 25°C for 22h. The mixture is diluted with dichloromethane and washed with water. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is 5 chromatographed on a silica gel column (15X2.5cm) using 1% increasing to 8% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.0272g; 19% yield), CIMS: m/z 433 (MH⁺).

FPT IC₅₀ = 9.24 μM

δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.2
	CH:	146.1, 139.5, 130.9, 123.4, 126.1, 132.4, 80.2
	C:	141.3, 135.2, 136.7, 134.0, 158.1
Piperidine	CH ₂ :	29.0, 51.4, 51.2, 28.7
	CH:	44.3
	C:	175.3
Piperidine N-substituent	CH:	150.6, 113.9, 113.9, 150.6
	C:	146.1

10

EXAMPLE 2. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-pyridinyl)-4-piperidinecarboxamide

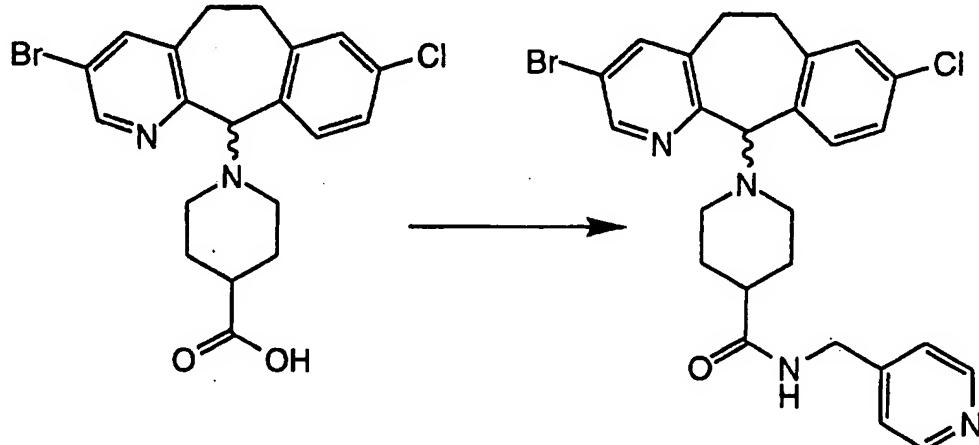


15 1-[3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-piperidinecarboxylate (0.25g) (1 equivalent) (prepared as described in Preparative Example 2 below) dissolved in anhydrous DMF (9ml) is added to a solution of 4-aminopyridine (0.0761g) (1.5 equivalents), DEC (0.155g) (1.5 equivalents), HOBT (0.1093g) (1.5 equivalents) and N-methylmorpholine (0.0889ml) (1.5 equivalents) in anhydrous DMF (4ml) and the mixture is stirred at 25°C for 42h. The solution is evaporated to dryness and the residue is 20

taken up in dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 1.5% increasing to 3% (10% concentrated 5 ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.0308g; 12%), CIMS: m/z 511 (MH⁺).
 FPT Inhibition = 0% @ 0.39 μM

δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 29.9
	CH:	146.9, 141.3, 132.2, 126.1, 130.5, 79.4
	C:	119.8, 140.7, 134.0, 136.1, 136.7, 156.5
Piperidine	CH ₂ :	29.0, 51.2, 51.5, 30.4
	CH:	44.5
	C:	174.6
Piperidine N-substituent	CH:	150.5, 113.8, 113.8, 150.5
	C:	145.9

EXAMPLE 3. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-10 benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-pyridinylmethyl)-4-piperidinecarboxamide



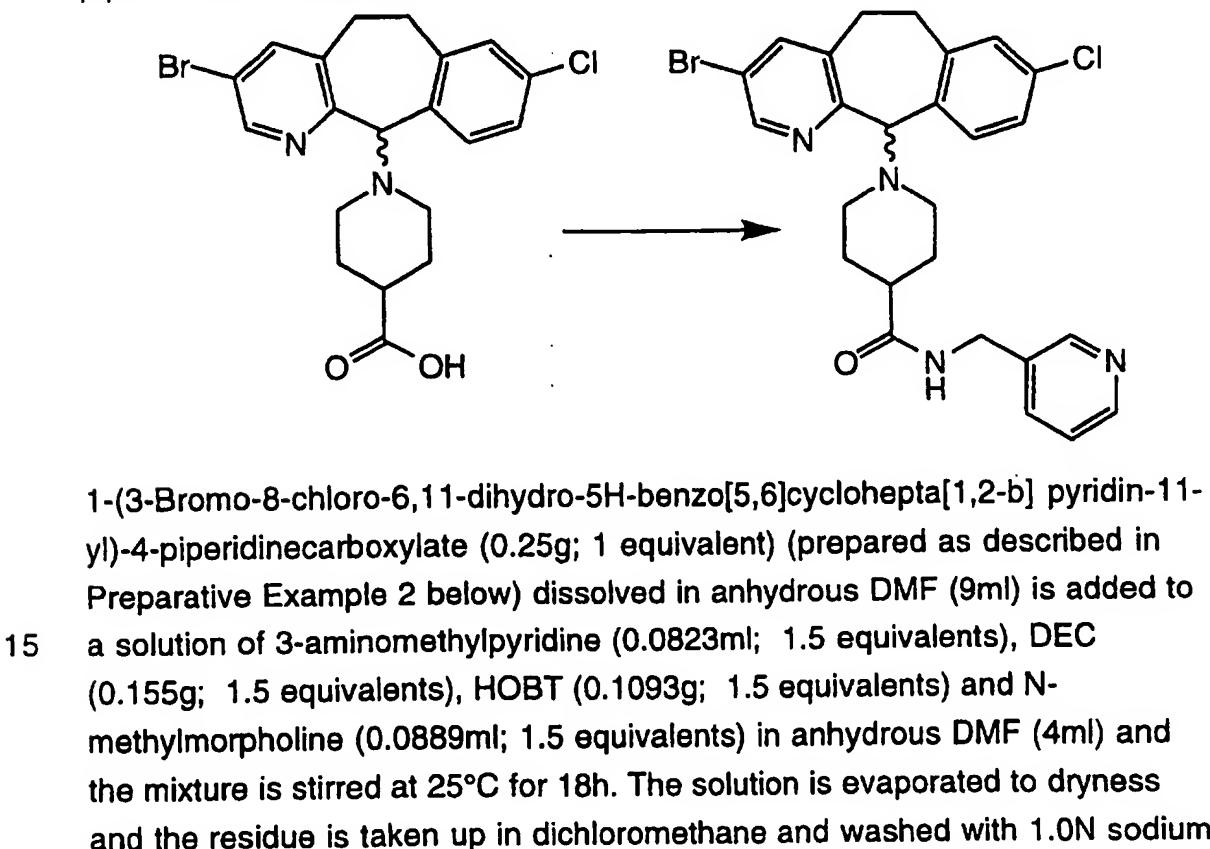
1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-4-piperidinecarboxylate (0.25g; 1 equivalent) (prepared as described in 15 Preparative Example 2 below) dissolved in anhydrous DMF (9ml) is added to a solution of 4-aminomethylpyridine (0.0821ml; 1.5 equivalents), DEC (0.155g; 1.5 equivalents), HOBT (0.1093g; 1.5 equivalents) and N-methylmorpholine (0.0889ml; 1.5 equivalents) in anhydrous DMF (4ml) and the mixture is stirred at 25°C for 19h. The solution is evaporated to dryness 20 and the residue is taken up in dichloromethane and washed with 1.0N sodium

hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (30X2.5cm) using 2% increasing to 3% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.2128g; 75% yield), FABMS: m/z 524.9 (MH⁺).

5 FPT Inhibition = 21% @ 1.1 μM

δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.3
	CH:	146.9, 141.2, 132.2, 126.1, 130.6, 79.4
	C:	119.9, 140.7, 134.0, 136.1, 136.7, 156.5
Piperidine	CH ₂ :	29.2, 51.4, 51.6, 29.2
	CH:	43.3
	C:	175.3
Piperidine N-substituent	CH ₂ :	42.1
	CH:	122.3, 149.9, 149.9, 122.3
	C:	147.7

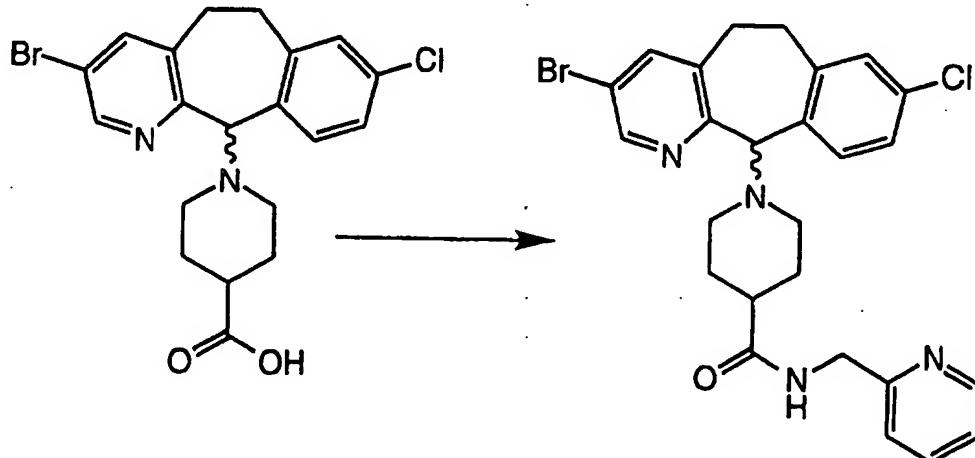
EXAMPLE 4. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridinylmethyl)-4-piperidinecarboxamide



hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 2% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.246g; 87%), FABMS: m/z 525 (MH⁺).
 5 FPT IC₅₀ = 1.3 μ M

δ_{C} (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.3
	CH:	146.9, 141.3, 132.3, 126.1, 130.6, 79.4
	C:	119.9, 140.7, 134.0, 136.2, 136.7, 156.6
Piperidine	CH ₂ :	29.2, 51.4, 51.7, 29.2
	CH:	43.4
	C:	175.2
Piperidine N-substituent	CH ₂ :	40.9
	CH:	149.1, 135.7, 123.7, 148.8
	C:	134.2

EXAMPLE 5. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(2-pyridinylmethyl)-4-piperidinecarboxamide
 10

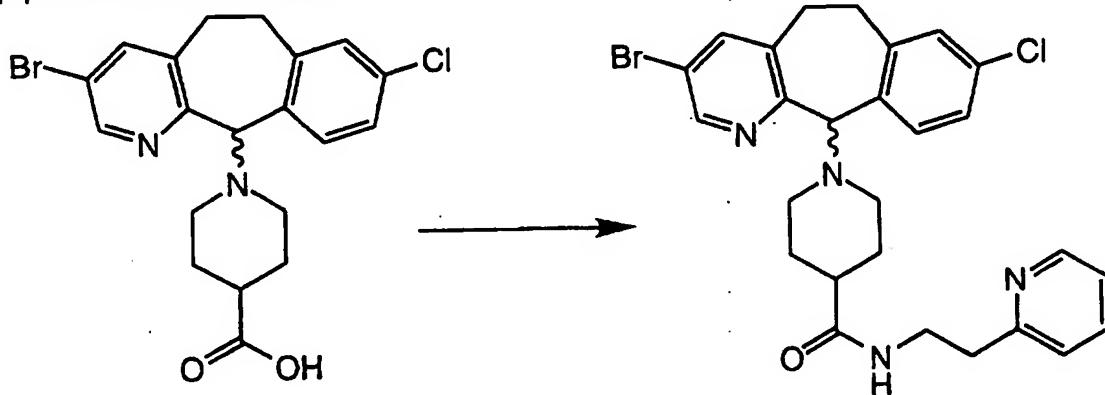


1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidinecarboxylate (0.25g; 1 equivalent) (prepared as described in Preparative Example 2 below) dissolved in anhydrous DMF (9ml) is added to a solution of 2-aminomethylpyridine (0.0834ml; 1.5 equivalents), DEC (0.155g; 1.5 equivalents), HOBT (0.1093g; 1.5 equivalents) and N-methylmorpholine (0.0889ml; 1.5 equivalents) in anhydrous DMF (4ml) and the mixture is stirred at 25°C for 18h.
 15

The solution is evaporated to dryness and the residue is taken up in dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 0.85% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.2475g; 87% yield), FABMS: m/z 525 (MH⁺).
 5 FPT IC₅₀ = 1.8 μM

δ_c (CDCl ₃)			
Tricyclic	CH ₂ :	30.4, 30.3	
	CH:	146.9, 141.2, 132.3, 126.1, 130.6, 79.5	
	C:	119.8, 140.7, 133.9, 136.3, 136.7, 156.7	
Piperidine	CH ₂ :	29.1, 51.5, 51.7, 29.1	
	CH:	43.4	
	C:	175.1	
Piperidine N-substituent	CH ₂ :	44.2	
	CH:	122.4, 137.1, 122.2, 148.9	
	C:	156.2	

EXAMPLE 6. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-
 10 benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(2-pyridinylethyl)-4-
 piperidinecarboxamide

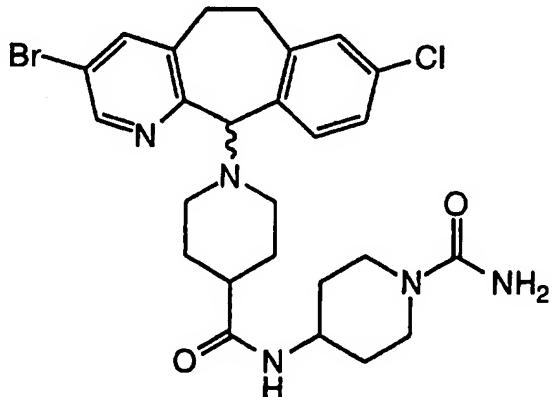


1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-
 15 yl)-4-piperidinecarboxylate (0.4g; 1 equivalent) (prepared as described in
 Preparative Example 2 below) dissolved in anhydrous DMF (14ml) is added to
 a solution of 2-aminoethylpyridine (0.134ml; 1.3 equivalents), DEC (0.215g;
 1.3 equivalents), HOBT (0.1515g; 1.3 equivalents) and N-methylmorpholine
 (0.123ml; 2.6 equivalents) in anhydrous DMF (6ml) and the mixture is stirred
 at 25°C for 67h. The solution is evaporated to dryness and the residue is
 20 taken up in dichloromethane and washed with 1.0N sodium hydroxide. The

dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 1% increasing to 2% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.4003g; 86% yield), FABMS: m/z 539.2 (MH⁺).
 5 FPT Inhibition = 9% @ 1.1 μM

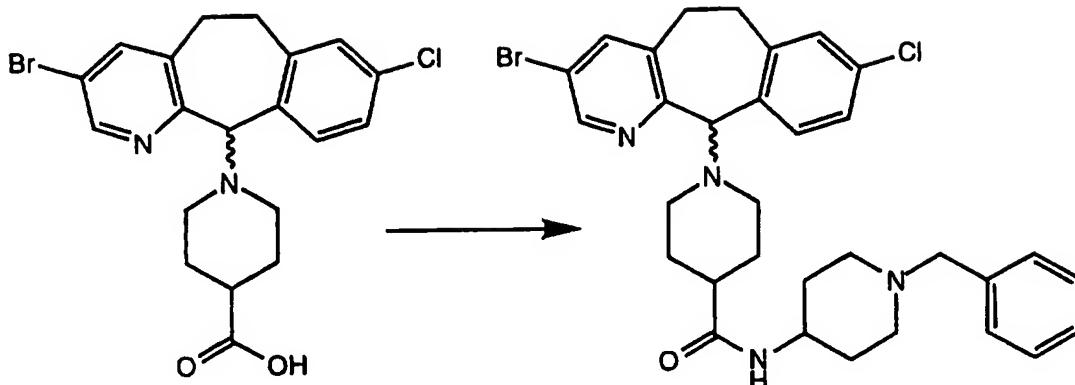
δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.3
	CH:	146.9, 141.2, 132.3, 126.1, 130.6, 79.5
	C:	119.8, 140.7, 133.9, 136.4, 136.7, 156.8
Piperidine	CH ₂ :	29.1, 29.1, 51.5, 51.7
	CH:	43.5
	C:	174.9
Piperidine N-substituent	CH ₂ :	38.6, 36.7
	CH:	123.6, 136.9, 121.7, 149.0
	C:	159.7

EXAMPLE 7. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-[4-(N-carboxamidopiperidinyl)]-4-piperidinecarboxamide
 10



Step A:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-[4-(N-benzylpiperidinyl)]-4-piperidinecarboxamide



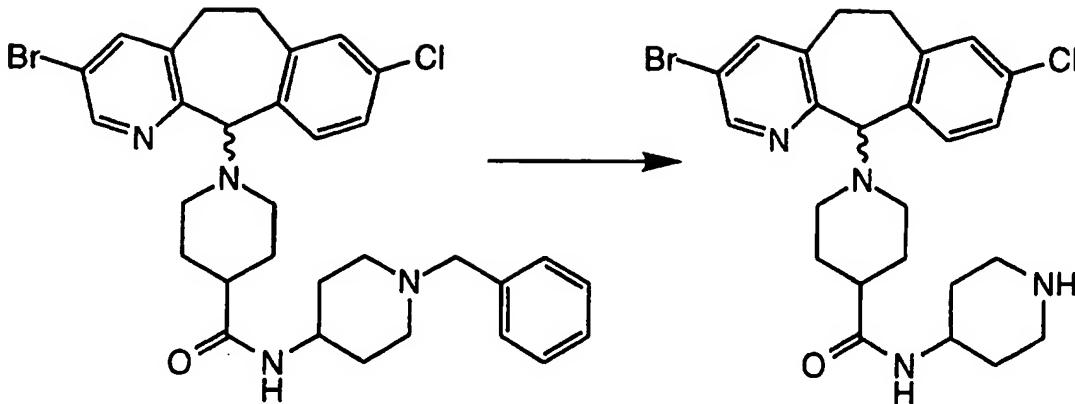
1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-4-piperidinecarboxylate (0.8g; 1 equivalent) (prepared as described in Preparative Example 2 below) dissolved in anhydrous DMF (29ml) is added to 5 a solution of 1-N-benzyl-4-aminopiperidine (0.4573ml) (1.3 equivalents), DEC (0.43g; 1.3 equivalents), HOBT (0.303g; 1.3 equivalents) and N-methylmorpholine (0.494ml; 2.6 equivalents) in anhydrous DMF (12.8ml) and the mixture is stirred at 25°C for 18h. The solution is evaporated to dryness and the residue is taken up in dichloromethane and washed with 1.0N sodium 10 hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 2% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.8143g; 78% yield), FABMS: m/z 607.1 (MH⁺).

15

δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.3
	CH:	146.9, 141.2, 132.2, 126.1, 130.6, 79.5
	C:	119.8, 140.7, 133.9, 136.3, 136.7, 156.8
Piperidine	CH ₂ :	29.2, 51.4, 51.7, 29.2
	CH:	43.6
	C:	174.3
Piperidine	CH ₂ :	52.3, 52.3, 32.3, 32.3, 63.0
N-substituent	CH:	46.3, 128.3, 128.3, 129.2, 129.2, 127.2
	C:	138.1

Step B:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-piperidinyl)-4-piperidinecarboxamide



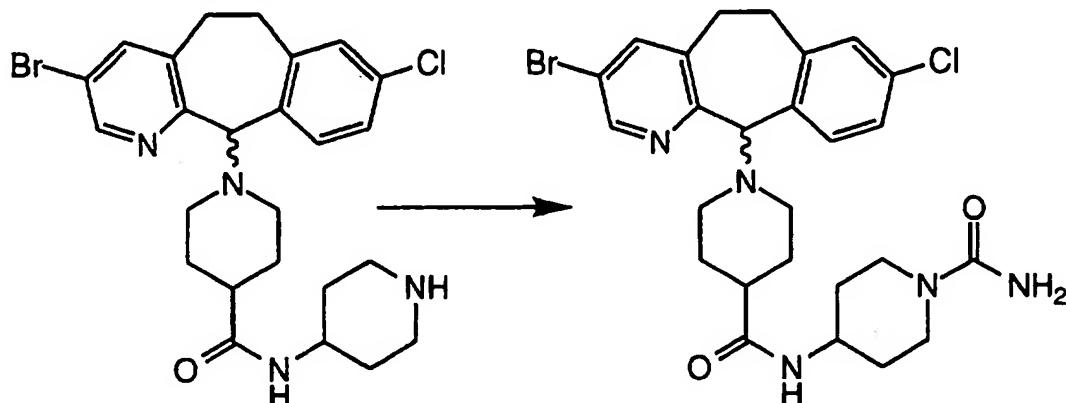
1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-[4-(N-benzylpiperidinyl)]-4-piperidinecarboxamide (0.51g; 1 equivalent) (prepared as described in Step A above) is dissolved in anhydrous

5 dichloromethane (3ml) and the solution is cooled to 0°C. α -Chloroethoxycarbonyl chloride (0.09027ml; 1 equivalent) is added over 5 minutes and the solution is allowed to warm to 25°C over 1h. The dichloromethane is removed *in vacuo* and anhydrous methanol (14ml) is added. The solution is heated under reflux for 1h. The solution is evaporated to dryness and the residue is taken up in dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 2.5% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give unreacted 1-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-[4-(N-benzylpiperidinyl)]-4-piperidinecarboxamide (0.1921g; 38% yield) and the title compound (0.199g; 46%), FABMS: m/z 517.5 (MH $^+$).

10
15
FPT Inhibition = 8.75% @ 0.39 μ M

δ_c (CDCl ₃ +CD ₃ OD)			
Tricyclic	CH ₂ :	30.3, 30.2	
	CH:	146.6, 141.4, 132.2, 126.1, 130.5, 79.2	
	C:	119.8, 140.6, 133.9, 136.1, 136.9, 156.7	
Piperidine	CH ₂ :	29.0, 51.4, 51.7, 29.0	
	CH:	43.4	
	C:	175.0	
Piperidine	CH ₂ :	44.9, 44.9, 32.0, 32.0	
N-substituent	CH:	46.0	

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]
cyclohepta[1,2-b]pyridin-11-yl)-N-[4-(N-carboxamidopiperidinyl)]-4-
piperidinecarboxamide

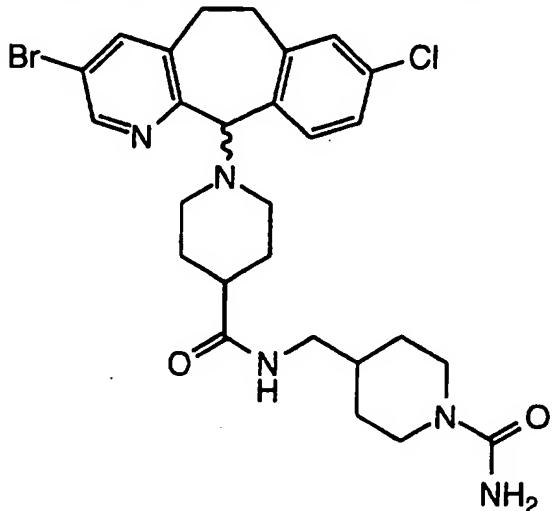


5 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinyl)-4-piperidinecarboxamide (0.1191g; 1 equivalent) (prepared as described in Step B above) is dissolved in anhydrous dichloromethane (3.3ml). Trimethylsilylisocyanate (0.467ml; 15 equivalents) is added and the mixture is stirred under argon at 25°C for 22h. Additional 10 trimethylsilylisocyanate (0.156ml; 5 equivalents) is added and the mixture is stirred for a total of 27h. The solution is diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (15X2.5cm) using 4% 15 (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.0678g; 53% yield), FABMS: m/z 560 (MH⁺). FPT Inhibition = 15% @ 0.36 μM

δ_c (CDCl ₃)			
Tricyclic	CH ₂ :	30.4, 30.3	
	CH:	146.8, 141.2, 132.2, 126.1, 130.6, 79.4	
	C:	119.8, 140.7, 133.9, 136.2, 136.7, 156.7	
Piperidine	CH ₂ :	29.1, 51.4, 51.7, 29.1	
	CH:	43.5	
	C:	174.7	
Piperidine N-substituent	CH ₂ :	43.3, 43.3, 31.9, 31.9	
	CH:	46.3	
	C:	158.1	

20 EXAMPLE 8. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]

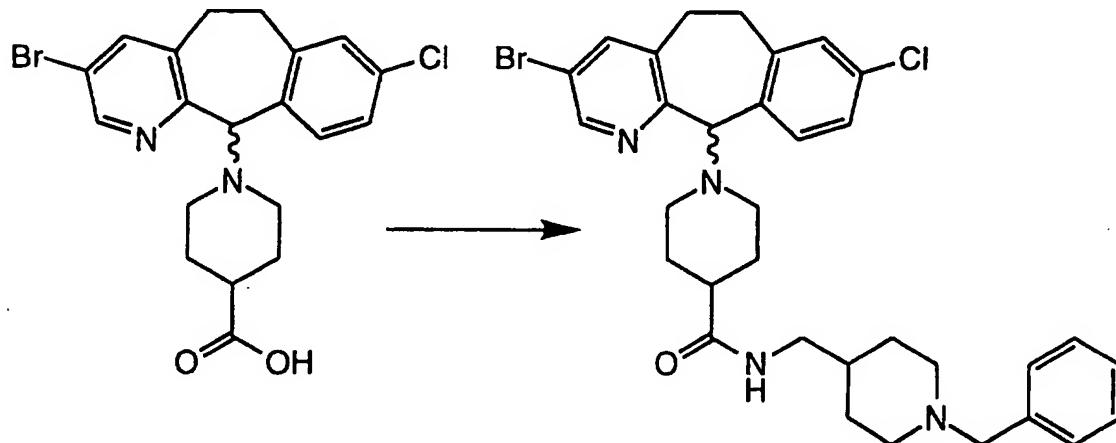
pyridin-11-yl)-N-[4-(N-carboxamidopiperidinyl)methyl]-4-piperidinecarboxamide



Procedure 1, Step A:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]

5 cyclohepta[1,2-b]pyridin-11-yl)-N-[4-(N-benzylpiperidinyl)methyl]-4-piperidinecarboxamide



1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-4-piperidinecarboxylate (0.8g; 1 equivalent) (prepared as described in

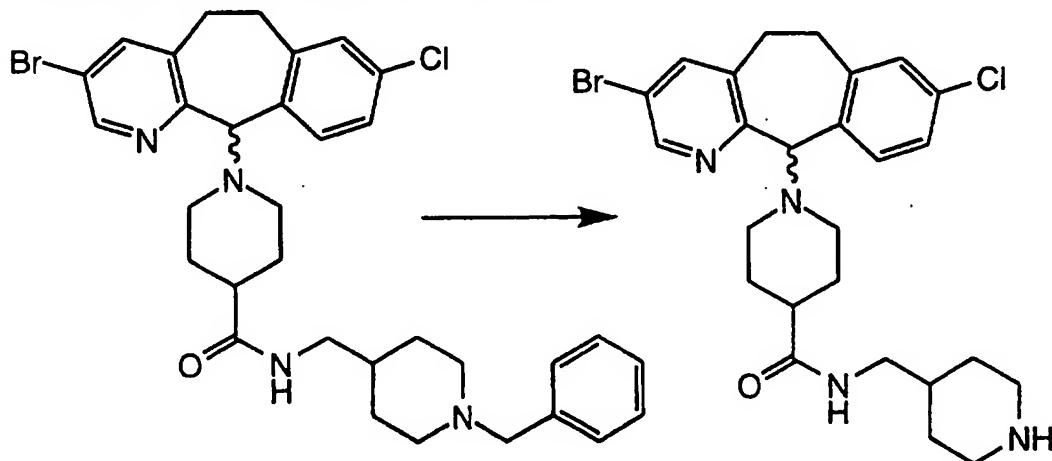
10 Preparative Example 2 below) dissolved in anhydrous DMF (29ml) is added to a solution of 1-N-benzyl-4-aminomethylpiperidine (0.4581g; 1.3 equivalents) (prepared as described in Preparative Example 4, Step B below), DEC (0.43g) (1.3 equivalents), HOBT (0.303g; 1.3 equivalents) and N-methylmorpholine (0.493ml; 2.6 equivalents) in anhydrous DMF (12.8ml) and 15 the mixture is stirred at 25°C for 24h. The solution is evaporated to dryness and the residue is taken up in dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 2% (10% concentrated ammonium

hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.7475g; 70% yield), FABMS: m/z 621.6 (MH⁺).

δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.3
	CH:	146.9, 141.2, 132.2, 126.1, 130.6, 79.5
	C:	119.8, 140.7, 133.9, 136.3, 136.7, 156.8
Piperidine	CH ₂ :	29.3, 51.5, 51.8, 29.3
	CH:	43.7
	C:	175.1
Piperidine N-substituent	CH ₂ :	53.3, 29.9, 29.9, 53.3, 63.4, 44.9
	CH:	36.0, 128.2, 129.2, 127.0, 129.2, 128.2
	C:	138.3

5 Step B:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-piperidinyl)-4-piperidinecarboxamide



10 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-[4-(N-benzylpiperidinylmethyl)]-4-piperidinecarboxamide (0.568g; 1 equivalent) (prepared as described in Step A above) is dissolved in anhydrous dichloromethane (5.9ml) and the solution is cooled to 0°C. α -Chloroethoxycarbonyl chloride (0.487ml; 5 equivalents) is added over 30 minutes and the solution is allowed to warm to 25°C over 2.5h. The 15 dichloromethane is removed *in vacuo* and anhydrous methanol (14.2ml) is added. The solution is heated under reflux for 1.25h. The solution is evaporated to dryness and the residue is taken up in dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is

chromatographed on a silica gel column (30X2.5cm) using 2% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give unreacted 1-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-[4-(N-benzylpiperidinyl)]-4-piperidinecarboxamide (0.1487g; 23% yield) and the title compound (0.1932g; 34% yield), FABMS: m/z 531.0 (MH⁺). The title compound is identical to that prepared in Procedure 2, Step B below. FPT Inhibition = 12% @ 0.38 μ M.

5

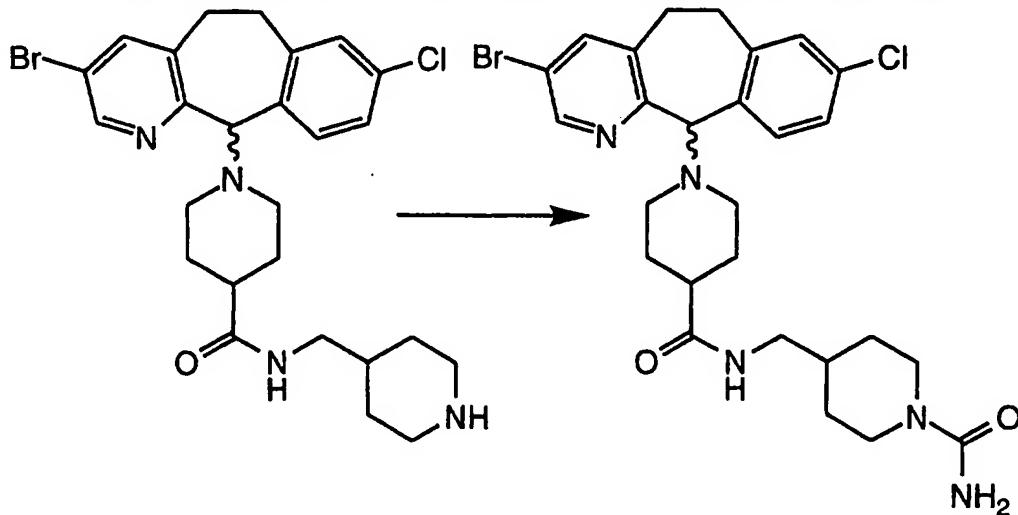
identical to that prepared in Procedure 2, Step B below. FPT Inhibition = 12% @ 0.38 μ M.

δ_c (CDCl ₃)			
Tricyclic	CH ₂ :	30.4, 30.3	
	CH:	146.9, 141.2, 132.2, 126.1, 130.6, 79.5,	
	C:	119.8, 140.7, 133.9, 136.3, 136.7, 156.7	
Piperidine	CH ₂ :	29.3, 51.5, 51.7, 29.3	
	CH:	43.7	
	C:	175.2	
Piperidine N-substituent	CH ₂ :	30.9, 30.9, 46.2, 46.2, 45.2	
	CH:	36.5	

10

StepC:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-[4-(N-carboxamidopiperidinyl)methyl]-4-piperidinecarboxamide



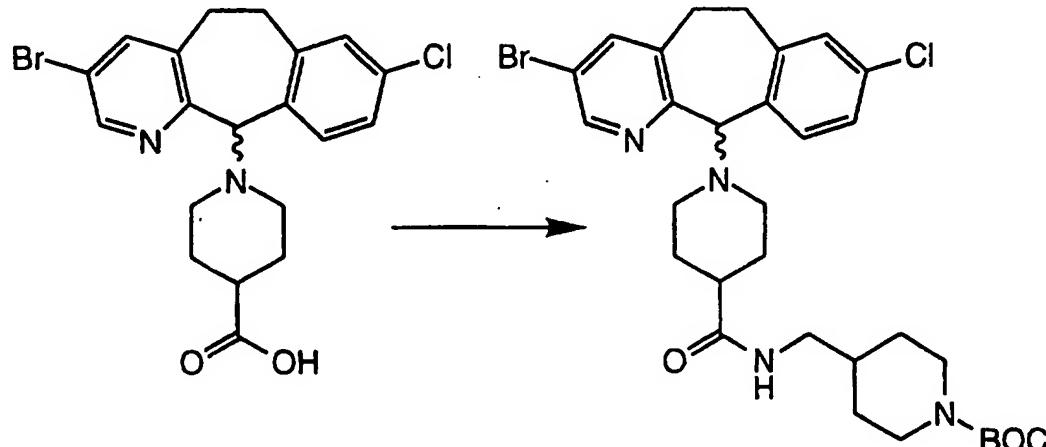
15

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (0.005g; 1 equivalent) (prepared as described in Step B above) is dissolved in anhydrous dichloromethane (0.161ml). Trimethylsilylisocyanate (0.0038ml; 3 equivalents) is added and the mixture is stirred at 25°C under argon for 16h.

The mixture is diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness to give the title compound which is identical on thin layer chromatography (TLC) to that prepared in Procedure 2, Step C below.

5 Procedure 2, Step A:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridin-11-yl)-N-[4-(N-*tert*-butoxycarbonylpiperidine)methyl]-4-piperidinecarboxamide



10

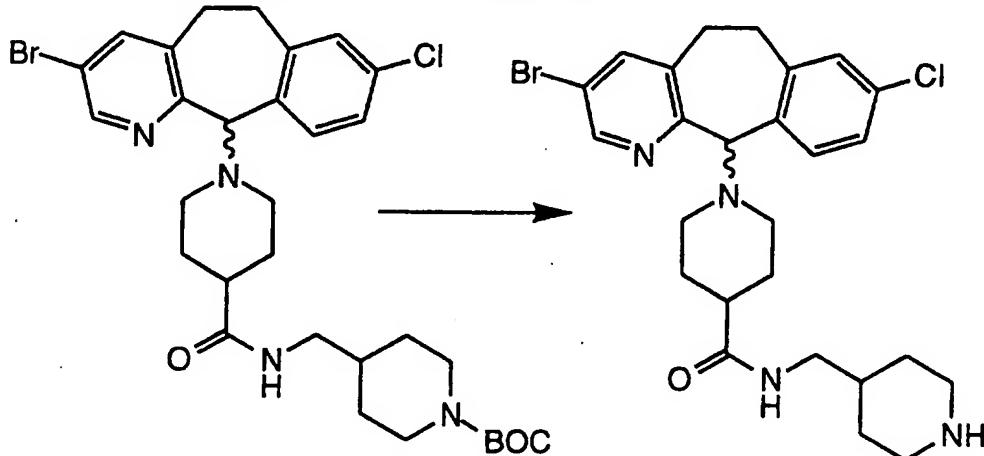
1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidinecarboxylate (0.5g; 1 equivalent) (prepared as described in Preparative Example 2 below) dissolved in anhydrous DMF (18ml) is added to 15 a solution of 1-N-*tert*-butoxycarbonyl-4-aminomethylpiperidine (0.1778g; 1 equivalent) (prepared as described in Preparative Example 3, Step C below), DEC (0.2067g; 1.3 equivalents), HOBT (0.1457g; 1.3 equivalents) and N-methylmorpholine (0.1185ml; 1.3 equivalents) in anhydrous DMF (8ml) and the mixture is stirred at 25°C for 19h. The solution is evaporated to dryness 20 and the residue is taken up in dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 0.75% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title 25 compound (0.4805g; 71% yield), FABMS: m/z 631 (MH⁺).

δ_c (CDCl₃)

Tricyclic	CH2:	30.4, 30.3
	CH:	146.9, 141.2, 132.2, 126.1, 130.6, 79.5
	C:	119.8, 140.7, 133.9, 136.3, 136.7, 156.7
Piperidine	CH2:	29.8, 51.7, 51.4, 29.3
	CH:	43.6
	C:	175.2
Piperidine N-substituent	CH3:	28.5
	CH2:	43.6, 43.6, 29.3, 29.3, 44.7
	CH:	36.4
	C:	79.5, 154.8

Step B:

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]hepta[1,2-b]pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide



5

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-[4-(N-*tert*-butoxycarbonylpiperidine)methyl]-4-piperidine carboxamide (0.3936g; 1 equivalent) is dissolved in anhydrous dichloromethane (30ml).

10 Trifluoroacetic acid (6.039ml; 127 equivalents) is added to the stirred solution at 0°C under argon. The mixture is stirred at 0°C for 1.5h and then allowed to warm to 25°C for 1h. The mixture is diluted with dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 7% increasing to 15 10% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.2023g; 61% yield), FABMS: m/z 531.1 (MH⁺).

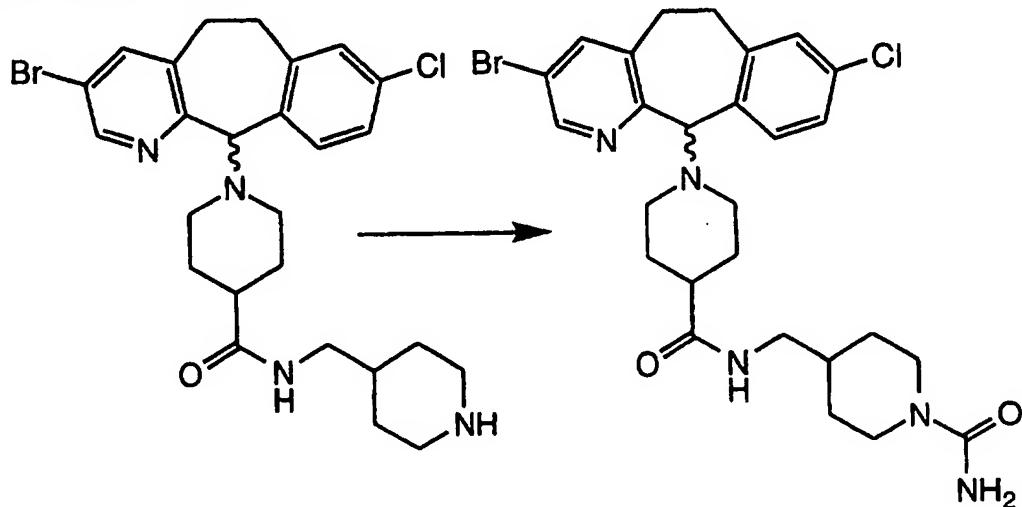
δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.3
	CH:	146.9, 141.2, 132.2, 126.1, 130.6, 79.5
	C:	119.8, 140.7, 133.9, 136.3, 136.7, 156.7
Piperidine	CH ₂ :	29.3, 51.4, 51.7, 29.3
	CH:	43.7
	C:	175.1
Piperidine N-substituent	CH ₂ :	30.7, 30.7, 46.1, 46.1, 45.2
	CH:	36.4

Step C.

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]

cyclohepta[1,2-b]pyridin-11-yl)-N-[4-(N-carboxamidopiperidinyl)methyl]-4-

5 piperidinecarboxamide

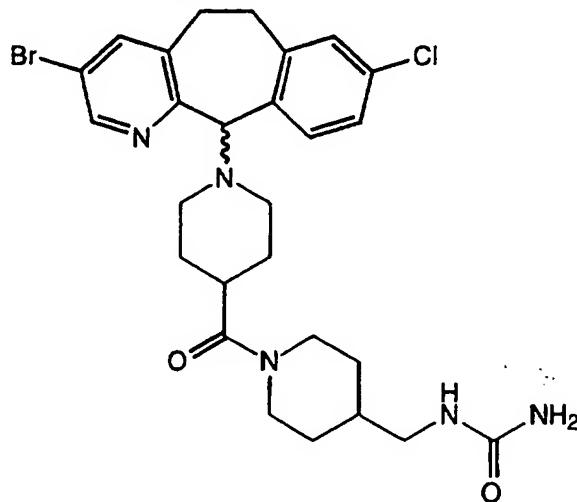


1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (0.140g; 1 equivalent) (prepared as described in Step B above) is dissolved in anhydrous dichloromethane (4.5ml). Trimethylsilylisocyanate (0.534ml) (15 equivalents) is added and the mixture is stirred at 25°C under argon for 18h. The mixture is diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (30X2.5cm) using 4% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.1084g; 72% yield), FABMS: m/z 573.9 (MH⁺). FPT Inhibition = 41% @ 1.04 μ M

δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.3
	CH:	146.8, 141.2, 132.2, 126.1, 130.6, 79.5
	C:	119.8, 140.7, 133.9, 136.3, 136.7, 156.7
Piperidine	CH ₂ :	29.3, 51.4, 51.7, 29.3
	CH:	43.5
	C:	175.4
Piperidine N-substituent	CH ₂ :	29.6, 29.6, 44.6, 44.6, 44.1
	CH:	36.1
	C:	158.1

EXAMPLE 9. 1-[1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidinylcarbonyl]-4-[(1-aminomethanamido)methyl]piperidine

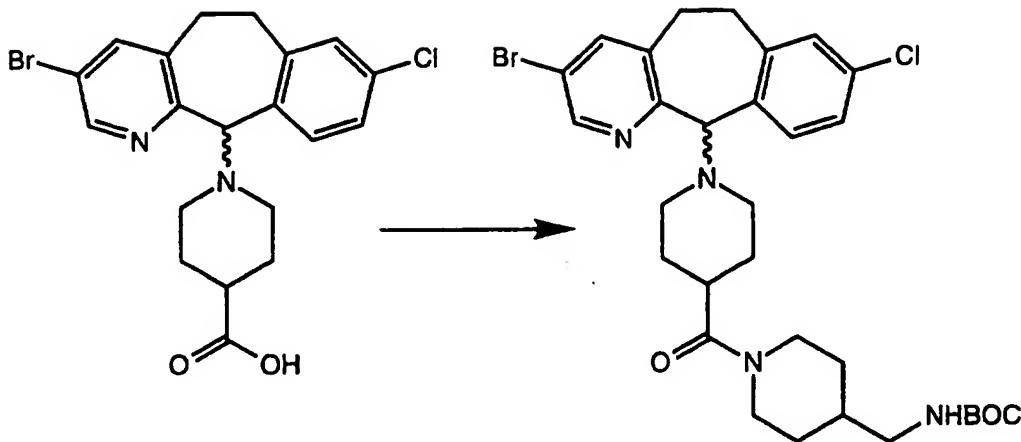
5



Step A:

1-[1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidinylcarbonyl]-4-[(N-*tert*-butoxycarbonylamino)methyl]piperidine

10

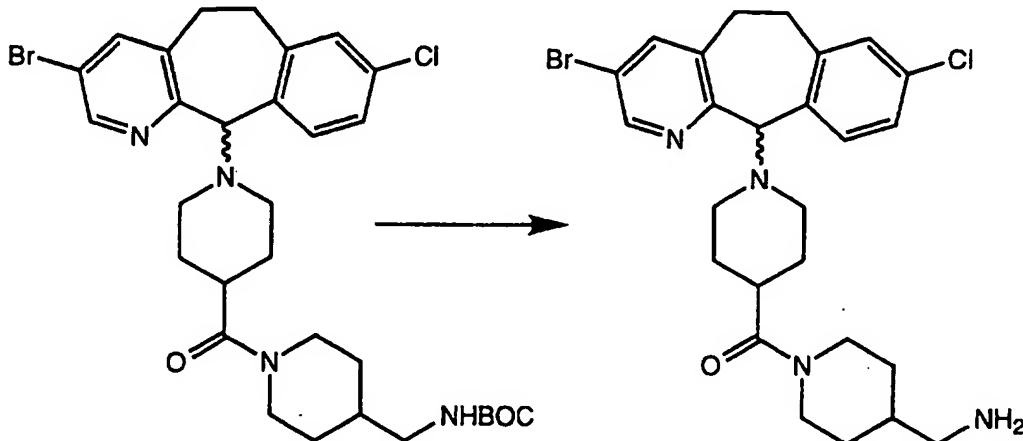


1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-4-piperidinecarboxylate (0.3195g; 1 equivalent) (prepared as described in Preparative Example 2 below) dissolved in anhydrous DMF (11.5ml) is added 5 to a solution of 4-[(N-*tert*-butoxycarbonylamino)-methyl]piperidine (0.1904g; 1.3 equivalents) (prepared as described in Preparative Example 5, Step C below), DEC (0.1703g; 1.3 equivalents), HOBT (0.1201g; 1.3 equivalents) and N-methylmorpholine (0.195ml; 2.6 equivalents) in anhydrous DMF and the mixture is stirred at 25°C for 19h. The solution is evaporated to dryness 10 and the residue is taken up in dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60X2.5cm) using 0.8% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title 15 compound (0.3701g; 86% yield), FABMS: m/z 631.3 (MH⁺).

δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.7, 30.4
	CH:	146.8, 141.2, 132.2, 126.0, 130.6, 79.6
	C:	119.7, 140.7, 133.8, 136.4, 136.7, 156.9
Piperidine	CH ₂ :	51.6, 29.1, 28.9, 51.9
	CH:	38.8
	C:	173.4
Piperidine N-substituent	CH ₃ :	28.4
	CH ₂ :	45.3/45.9, 28.9/29.1, 29.5/30.2, 45.3/45.9, 41.7
	CH:	37.0
	C:	79.4, 156.1

Step B:

1-[1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-[piperidinyl]-4-aminomethylpiperidine

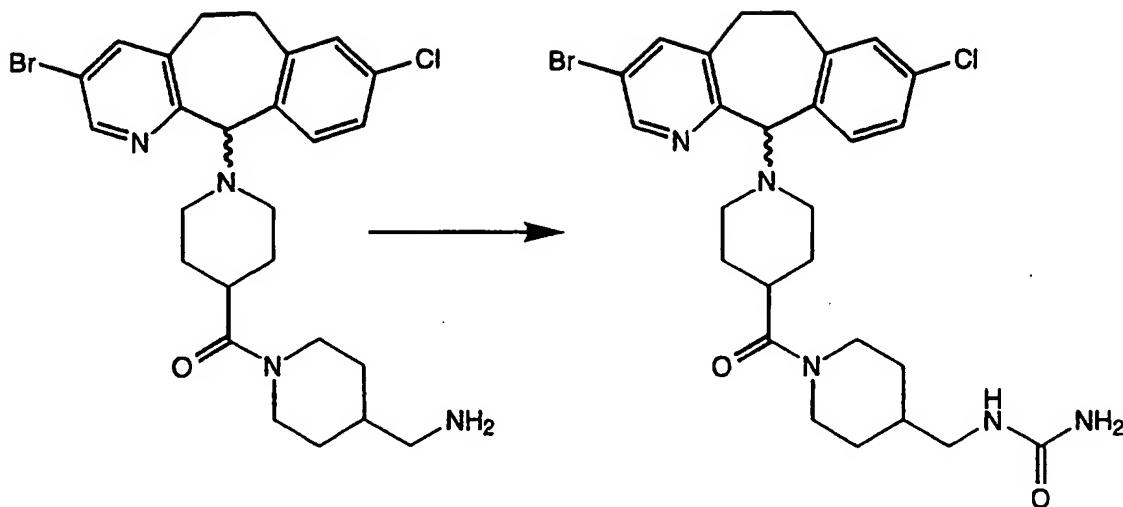


1-[1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta [1,2-b] pyridin-11-yl)-4-piperidinylcarbonyl]-4-[(N-*tert*-butoxycarbonylamino)methyl]piperidine (0.35g) (1 equivalent) is dissolved in methanol (3.1ml). A 10% (v/v) solution of concentrated sulfuric acid in dioxane (7.568ml) is added and the mixture is stirred at 25°C under argon for 1.5h. The mixture is stirred at 0°C for 1.5h and then allowed to warm to 25°C for 1h. The mixture is diluted with dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (30X2.5cm) using 4% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.226g; 77% yield), FABMS: m/z 531.4 (M⁺). FPT Inhibition = 16% @ 0.38 μM

δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.2
	CH:	146.8, 141.2, 132.2, 126.0, 130.6, 79.6
	C:	119.8, 140.7, 133.8, 136.4, 136.7, 156.9
Piperidine	CH ₂ :	51.6, 29.1, 28.9, 51.9
	CH:	38.8
	C:	173.3
Piperidine N-substituent	CH ₂ :	42.0, 29.7/30.9, 29.0/29.2, 42.0, 45.5
	CH:	38.8

Step C:

1-[1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidinylcarbonyl]-4-[(1-aminomethanamido)methyl]piperidine

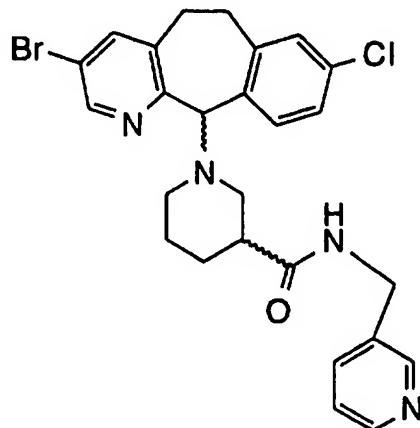


1-[1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta [1,2-b] pyridin-11-yl)-4-piperidinylcarbonyl]-4-[(N-*tert*-butoxycarbonylamino)methyl]piperidine (0.185g) (1 equivalent) (prepared as described in Example 9, Step B above) is dissolved in anhydrous dichloromethane (5ml). Trimethylsilylisocyanate (0.706ml) (15 equivalents) is added and the mixture is stirred at 25°C under argon for 22h. Additional trimethylsilylisocyanate (0.235ml) (5 equivalents) is added and the stirring is continued for a total of 26.75h. The mixture is diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (30X2.5cm) using 3.5% (10% concentrated ammonium hydroxide in methanol)-dichloromethane to give the title compound (0.1502g; 75% yield), FABMS: m/z 574.2 (MH⁺).

15 FPT IC₅₀ = 0.66 μM

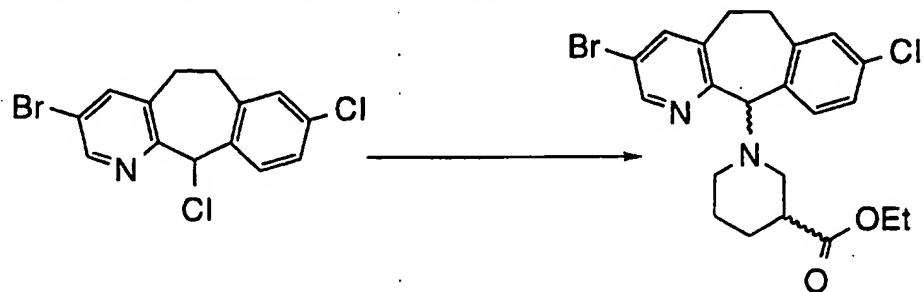
δ_c (CDCl ₃)		
Tricyclic	CH ₂ :	30.4, 30.2
	CH:	146.8, 141.2, 132.2, 126.1, 130.6, 79.5
	C:	119.8, 140.7, 133.9, 136.2, 136.7, 156.7
Piperidine	CH ₂ :	51.5, 29.0, 28.9, 51.8
	CH:	38.8
	C:	173.6
Piperidine N-substituent	CH ₂ :	41.9, 41.9, 30.7, 29.6, 45.4
	CH:	36.9
	C:	159.2

EXAMPLE 10. 1-(8-chloro-3-bromo-5,6-dihydro-11H-benzo[5,6]-cyclohepta[1,2-b]pyridin-11-yl)piperidine-3-(N-3-pyridylmethylamino)carboxamide



5 Procedure 1, Step A.

Ethyl 1-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-3-piperidinecarboxylate

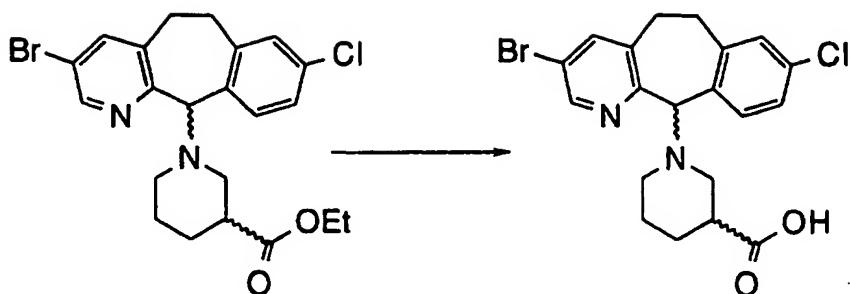


3-Bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

10 (1g, 2.5 mmol) is dissolved in 10 mL of N,N-dimethylformamide (DMF). Ethynipeacetate (0.6 ml, 3.7 mmol) and N-methylmorpholine (0.69 mL, 6.2 mmol) are added and the reaction mixture is stirred at ambient temperature for 18 hours. The reaction mixture is poured into water and extracted with dichloromethane two times. The combined extracts are dried over magnesium sulfate and the mixture filtered and evaporated to obtain an oil. The oil is chromatographed on silica gel using 10% ethyl acetate/hexanes as the eluent to obtain 0.55 gm of the title compound. FABMS (MH⁺)=464

Step B.

20 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-3-piperidinecarboxylate

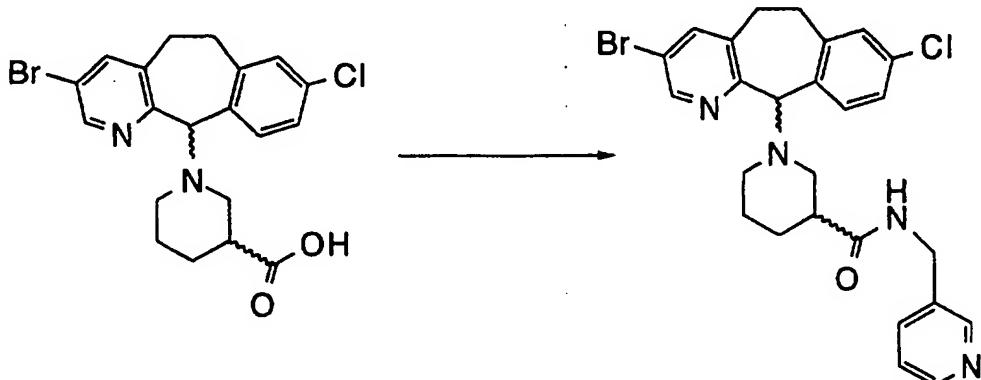


Ethyl 1-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-3-piperidinecarboxylate (1.9 gm) is refluxed in 25 ml of 6N hydrochloric acid for 8 hours. The HCl and water is evaporated to obtain the title compound, as a solid.

5

Step C.

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridinylmethyl)-3-piperidinecarboxamide



10

The compound from Example 10, Step B is dissolved in 12 mL of DMF and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DEC) (0.37 g 1.9 mmol), 1-hydroxybenzotriazole (HOBT) (0.36g), NMM (0.5 mL) and (0.216 g, 2.0 mmol) of 3-aminomethylpyridine are added and the reaction mixture is stirred at ambient temperature. After 17 hours the reaction mixture is poured into water and extracted with dichloromethane two times. The combined extracts are dried over magnesium sulfate and the mixture filtered and evaporated to obtain an oil. The oil is chromatographed on silica gel using 5% methanol/dichloromethane as the eluent to obtain 0.44 gm of the title compound.

15

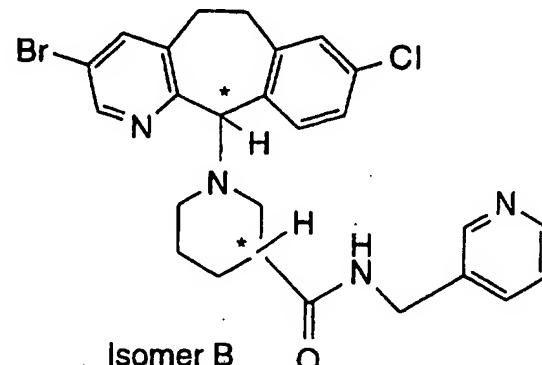
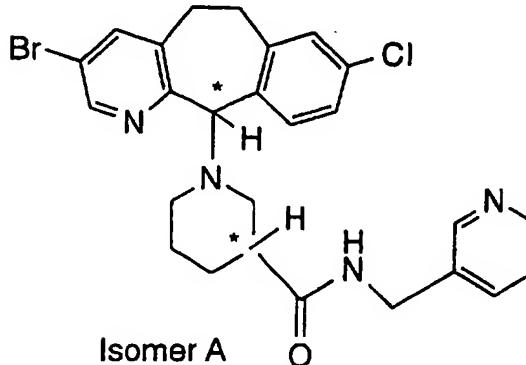
20

FABMS (MH⁺)=603

FPT IC₅₀ = 0.21 μ M

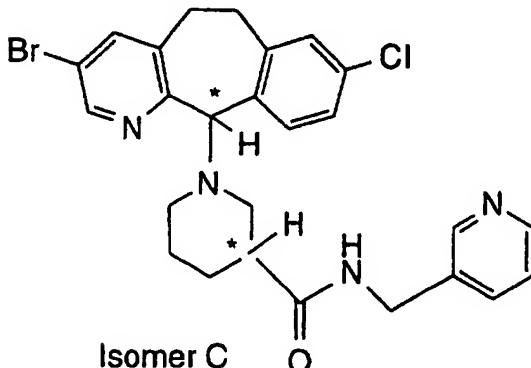
Step D. Separation of Isomers

The compound of Example 10, Procedure 1, Step C, is separated into its four optical isomers by HPLC chromatography with a Chiralpak® AD analytical (0.46cmX25cm) chiral column (amylose tris(3,5-dimethylphenyl carbamate) coated on a 10 μ M silica-gel substrate (trademark of Chiral Technologies, Exton, Pennsylvania), using as the eluting solvent, 20% isopropanol/hexanes/.02% diethylamine at 1mL/minute, the four compounds elute at 10.27 (Isomer A), 11.43 (Isomer B), 11.57 (Isomer C) and 18.37 (Isomer D) minutes.

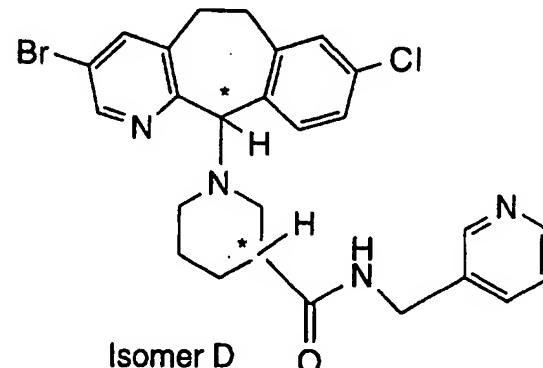


10 FABMS(MH^+)=526.8
FPT Inhibition = 6.1% @ 1.14 μ M

FABMS(MH^+)=526.8
FPT IC₅₀ = 0.194 μ M

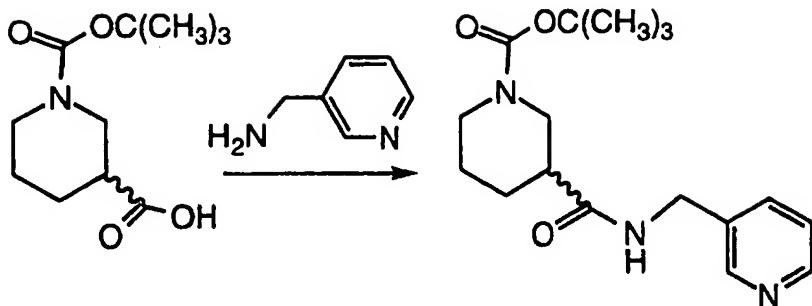


15 FABMS(MH^+)=526.8
FPT IC₅₀ = 0.179 μ M



FABMS(MH^+)=526.8
FPT IC₅₀ = 0.187 μ M

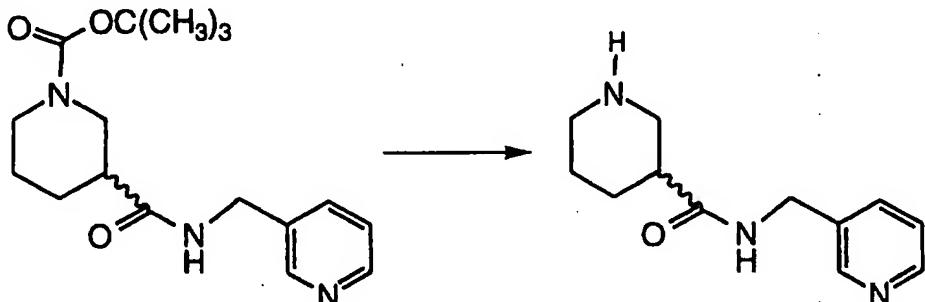
Procedure 2. Step A.



To a solution of N-(tert-butoxycarbonyl)nipecotic acid (0.50 g, 2.41 mmol) in dichloromethane (10 mL) is added 3-(aminomethyl)pyridine (0.27 mL, 2.65 mmol), 1-hydroxybenzotriazole monohydrate (HOBT) and 1,3-

5 dicyclohexylcarbodiimide (0.547 g, 2.65 mmol). The mixture is stirred at room temperature for 16 hr and is then filtered. The solution is purified by flash chromatography (SiO₂, 2% methanol in CH₂Cl₂) affording 0.67g of the product.

Step B.

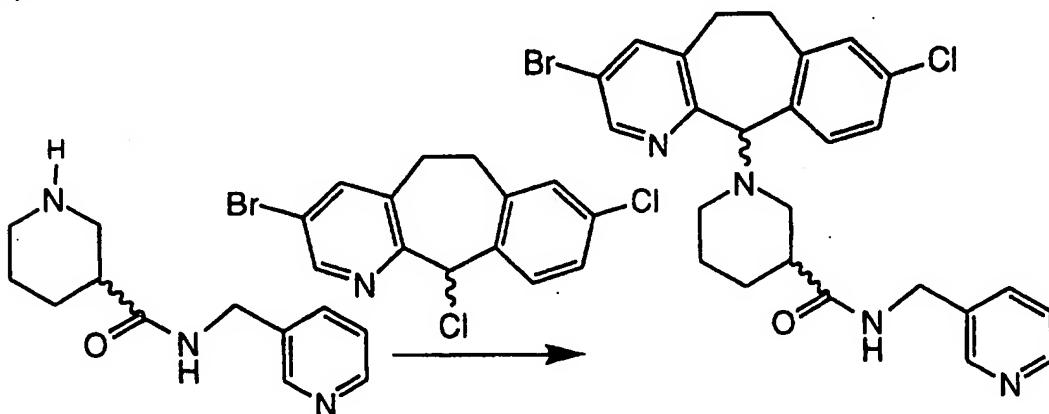


10

A solution of the product of Example 10, Procedure 2, Step A, (0.04g, 0.125 mmol) in CH₂Cl₂ (3 mL) is treated with trifluoroacetic acid (TFA) (0.5 mL) for 1 hr. The mixture is then evaporated to dryness in vacuo and azeotroped with methanol (3 x 5mL portions).

15

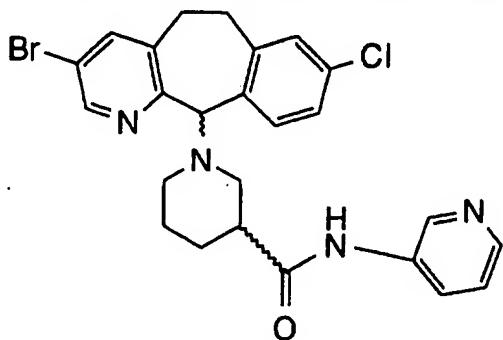
Step C.



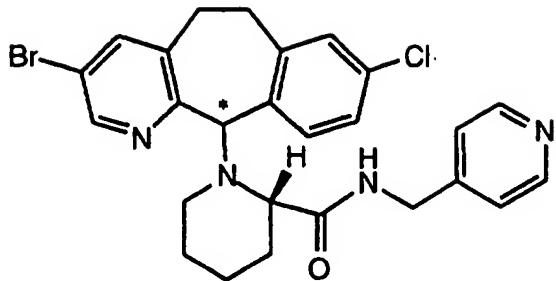
The residue from Example 10, Procedure 2, Step B above, is then dissolved in CH₃CN (1 mL) and a solution of 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (0.07 g, 0.2 mmol) in CH₃CN is added, followed by 1,2,2,6,6-pentamethylpiperidine (0.2 mL, 1.1 mmol). The solution 5 is heated at 45°C for 16 hr and then evaporated to dryness in vacuo. The residue is purified by flash chromatography (SiO₂, 3% methanol in CH₂Cl₂) affording 0.04g of the title compound.

1H NMR (300 MHz) CDCl₃; δ=1.45-1.75 (m, 2H); 1.8-1.92 (m, 1H); 2.02-2.15 (m, 1H); 2.16-2.30 (m, 1H); 2.38-2.52 (m, 2H); 2.58-2.72 (m, 2H); 3.16-3.3 (m, 10 1H); 3.46-3.70 (m, 2H); 3.70-3.82 (m, 1H); 4.32 (br. s, 2H); 4.39 (d, 1H); 4.45-4.52 (m, 1H); 6.93 (br. s, 0.5 H); 7.06-7.17 (m, 3H); 7.22-7.28 (m, 1H); 7.35 (br. s, 0.5H); 7.45-7.52 (m, 1H); 7.53 (d, 0.5H); 8.38 (d, 0.5H); 8.49 (br. s, 1H); 1.58 (m, 1H).

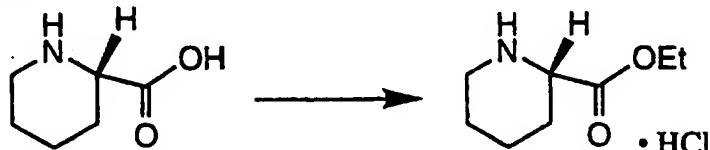
EXAMPLE 11. 1-(3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridinyl)-3-piperidinecarboxamide



EXAMPLE 12. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-pyridinylmethyl)-2S-piperidinecarboxamide- Isomer A1 amide



Step A1. L-Pipecolinic Acid Ethyl Ester Hydrochloride.

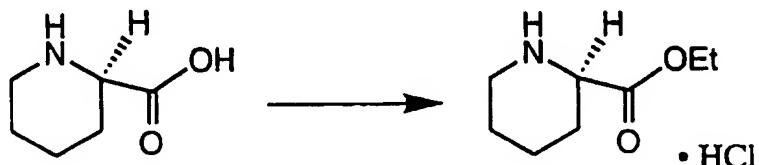


5

L-Pipecolinic acid (0.9g, 6.97 mmol) is dissolved in 40 mL of absolute EtOH. HCl gas is bubbled for ~1 minute. The reaction mixture is refluxed for 20 min, cooled and the solvents removed by rotary evaporation to give 1.34g of the title compound, a wax that is used without further purification.

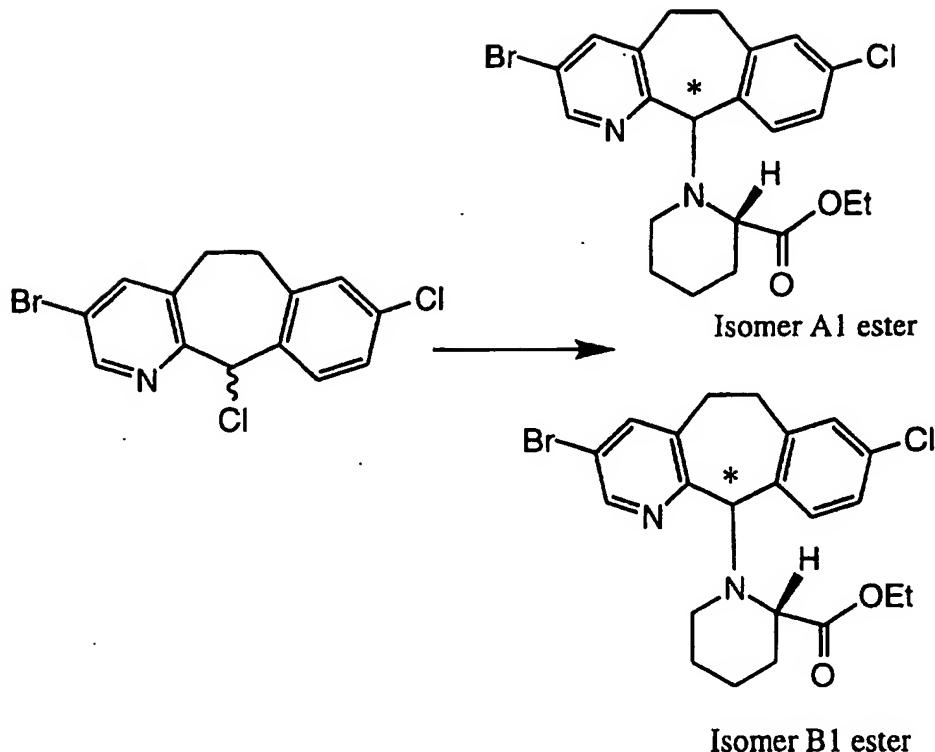
10

Step A2. D-Pipecolinic Acid Ethyl Ester Hydrochloride.



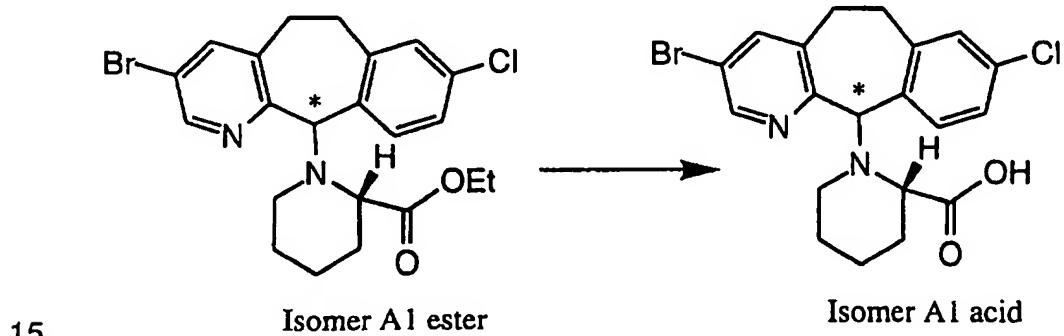
15 Using essentially the same conditions as described in Example 12, Step A1, but replacing L-Pipecolinic acid with D-Pipecolinic acid, the title compound is obtained.

Step B.



3-Bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (1.10 g, 3.00 mmol) and L-pipecolinic acid ethyl ester hydrochloride from Example 12, Step A1 (1.34 g, 6.98 mmol), triethylamine (2.91 μ L, 21 mmol) 5 are dissolved in dry CH_2Cl_2 (20ml) and the mixture is stirred at 25°C under nitrogen for 72h. The reaction mixture is washed with saturated NaHCO_3 , H_2O , brine and then filtered through Na_2SO_4 and evaporated to dryness. The product is chromatographed on a silica gel column using 1% ethyl acetate-dichloromethane as the eluant to separate the two separable diastereomeric 10 isomers (i.e. Isomers A1 ester and B1 ester), the less polar being referred to as Isomer A1 ester and the more polar isomer being referred to as Isomer B1 ester. FABMS $\text{MH}^+ = 464$.

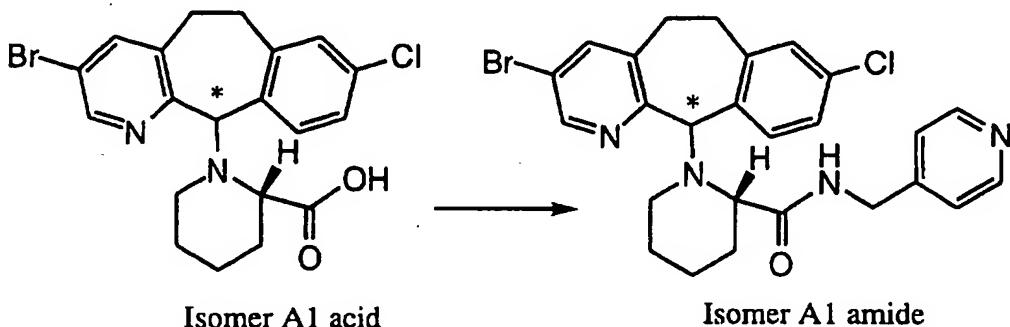
Step C.



Isomer A1 ester from Example 12, Step B (0.26g, 0.6 mmol) is dissolved in 6 mL of ethanol and 1.4 mL of 1M LiOH (1.4 mmol) is added. The reaction mixture is heated on oil bath at 80°C for 10h, cooled and 1.5 mL of 1N HCl is then added to adjust the pH to ~ 4.5. Solvents are then removed by evaporation and the resulting crude acid is used in the next reaction without further purification.

5

Step D.

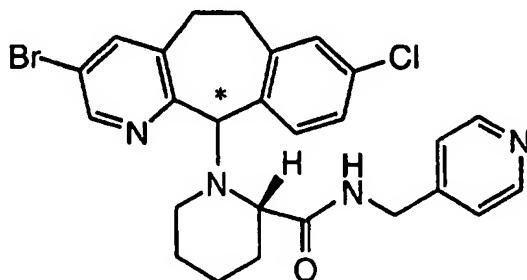


10 Isomer A1 acid from Example 12, Step C (from 0.26g, 0.6 mmol of Isomer A ester) is dissolved in 3 mL of DMF and NMM (184 μ L, 1.6 mmol), 4-(aminomethyl)pyridine (74 μ L, 0.078g, 0.73 mmol), HOBT(0.098 g, 0.72 mmol), DEC(0.139g, 0.72 mmol) are then added. The reaction mixture is stirred at room temperature for 16h. DMF is removed by rotary evaporation

15 and the resulting crude mixture is partitioned between EtOAc-NaHCO₃. The organic phase is washed with H₂O, brine and filtered through Na₂SO₄ to give crude product that is purified by flash chromatography eluting with 3% (10% NH₄OH-CH₃OH)-CH₂Cl₂ solvent system to obtain the title compound, a white solid FAB-MS MH⁺ = 527

20 FPT Inhibition = 18% @ 1.1 μ M

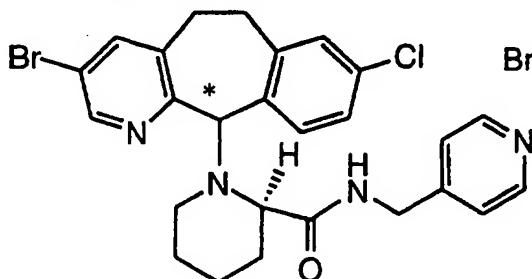
Example 13. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-pyridinylmethyl)-2S-piperidinecarboxamide - Isomer B1 amide



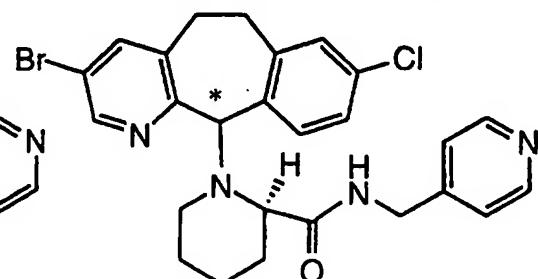
Using the method of Example 12, Steps C and D, except that Isomer B1 ester from Example 12, Step B, is used instead of Isomer A1 ester, the title compound is obtained. $MH^+ = 527$
 FPT Inhibition = 21% @ 1.1 μM

5

Example 14. Using the method of Examples 12 and 13, except that D-pipecolinic acid ethyl ester hydrochloride is used in place of L-pipecolinic acid ethyl ester hydrochloride, the following two diasteriomers are obtained:



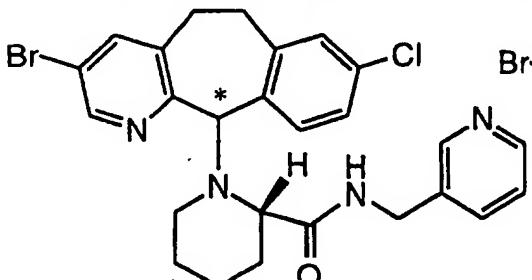
Isomer A2 amide



Isomer B2 amide

10 $MH^+ = 527$ FPT Inhibition = 0% @ 1.1 μM $MH^+ = 527$ FPT Inhibition = 13% @ 1.1 μM

Example 15. Using the method of Examples 12-14, except that in Example 12, Step D, 3-(aminomethyl)pyridine is used in place of 4-(aminomethyl)pyridine, the following four diasteriomers are prepared.

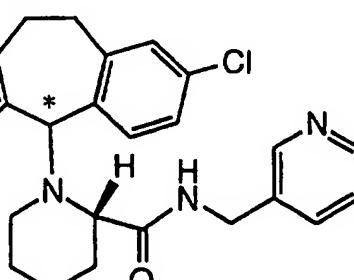


Isomer C1 amide

15

 $MH^+ = 527$

melting point (m.p.) = 198.5-199°C

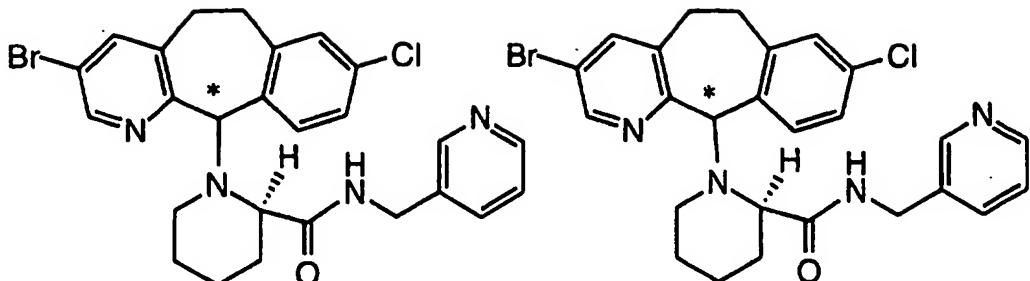
FPT IC₅₀ = 0.3 μM 

Isomer D1 amide

 $MH^+ = 527$

m.p. = 180.9-181.5°C

FPT IC₅₀ = 0.16 μM



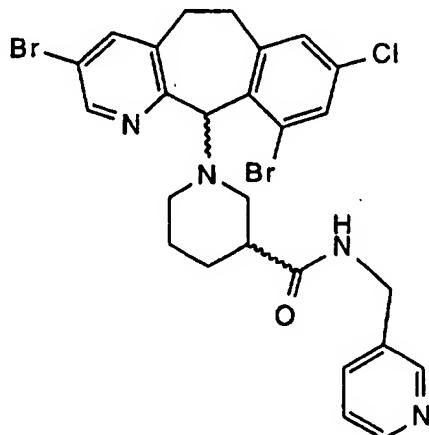
Isomer C2 amide

MH⁺ = 527
m.p. = 168.2-168.4°C
FPT Inhibition = 11% @ 0.38 μM

Isomer D2 amide

MH⁺ = 527
m.p. = 205.5-206.4°C
FPT Inhibition = 0% @ 0.38 μ M

5 Example 16. 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridinylmethyl)-3-piperidinecarboxamide



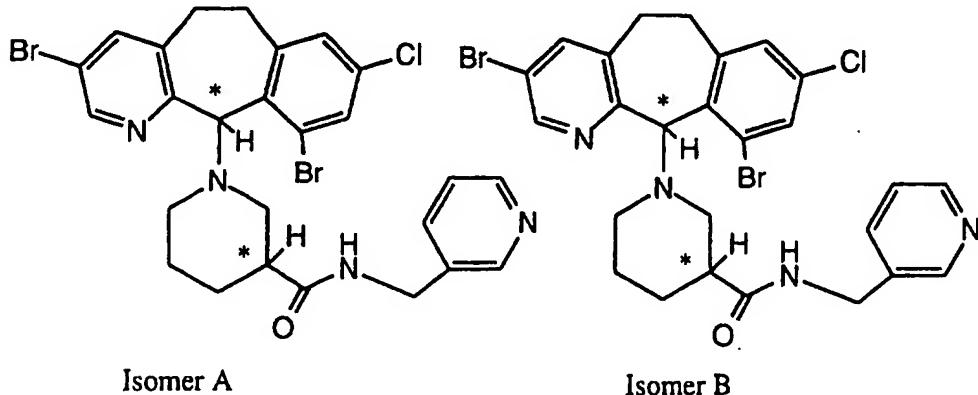
10 Using the method of Example 10, Procedure 1, except that the compound 3,10-dibromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is substituted for 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the title compound is obtained. FABMS $\text{MH}^+ = 605.7$
FPT $\text{IC}_{50} = 0.027\mu\text{M}$

15 EXAMPLE 17 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridinylmethyl)-3-piperidinecarboxamide

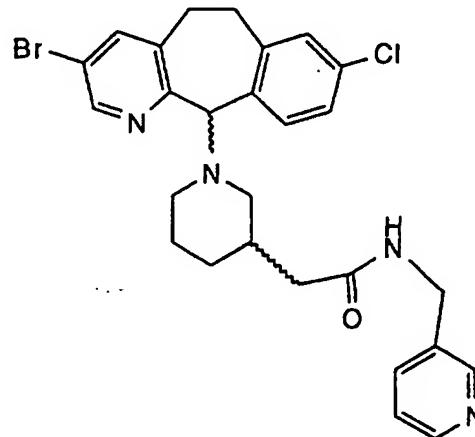
Using the method of Example 10, Procedure 1, except that the compound 3,10-dibromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is substituted for 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and optically pure ethynipecotate is

used, the title compound is obtained. Optically pure ethylnipecotate can be prepared from L-tartaric acid according to (Recl. Trav. Chim. P. 899, 1951).

5 Separation of the resulting two isomers by HPLC chromatography is performed on a Chiral Technologies AD analytical (0.46cmX25cm) chiral column using 10% isopropanol/hexanes/0.02% diethylamine at 1mL/minute. The two compounds are eluted at 14.85 (Isomer A) and 24.7 (Isomer B) minutes.

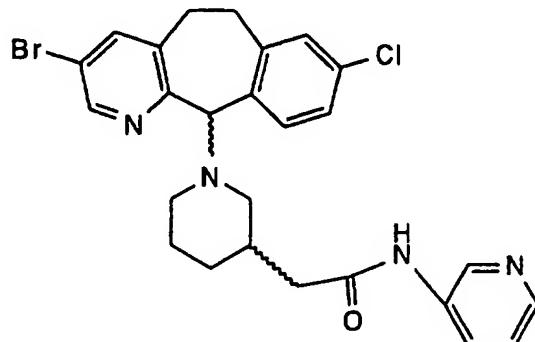


10 $MH^+ = 605.7$ $MH^+ = 605.7$
 FPT $IC_{50} < 0.0099 \mu M$ FPT Inhibition = 3.4% at 0.1 μM
 EXAMPLE 18. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridinylmethyl)-3-piperidineacetamide



15 Using the method of Example 10, Procedure 1, except that 3-ethylpiperidineacetate is substituted for ethylnipecotate, the title compound is obtained. $FABMS(MH^+) = 541.0$
 FPT Inhibition = 9% @ 1.1 μM

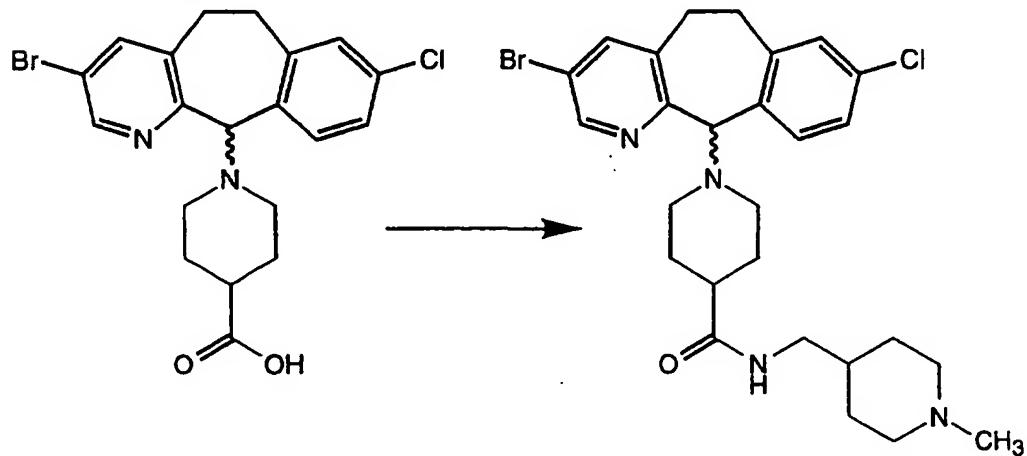
EXAMPLE 19. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridinyl)-3-piperidineacetamide



5 Using the method of Example 10, Procedure 1, except that 3-ethylpiperidineacetate is substituted for ethylnipecotate, and Example 11, except that nicotinic acid is substituted for 3-pyridylacetic acid, the title compound is obtained. FABMS(MH⁺)= 526.9
FPT Inhibition = 15% @ 1.1 μM

10

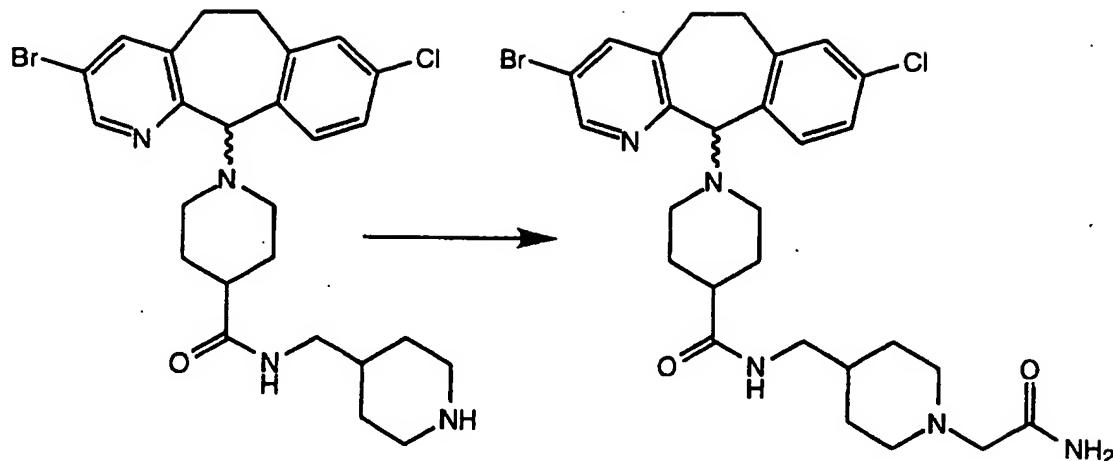
EXAMPLE 20.



15 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidinecarboxylate (1 equivalent) (prepared as described in Preparative Example 2) is reacted with 1-N-methyl-4-(aminomethyl)-piperidine (1.3 equivalents) (prepared by reductive formylation of 4-ethoxycarbonylaminomethylpyridine, followed by hydrolysis of the protecting group under standard conditions) under similar conditions to those described in Preparative Example 2, below, to give the title compound.

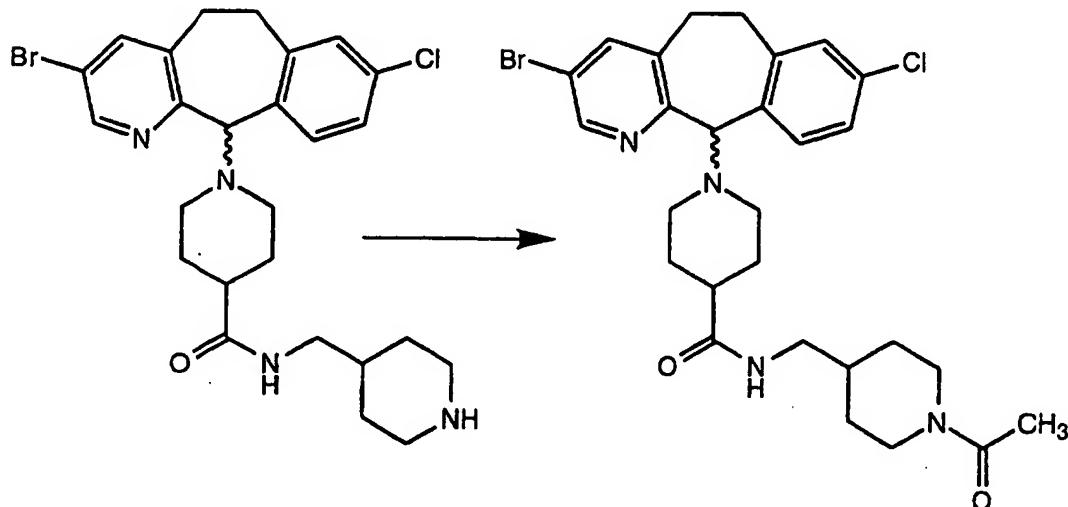
20

EXAMPLE 21



5 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) is reacted with 2-bromoacetamide (1.1 equivalents) and sodium carbonate in anhydrous DMF at 25°C to give the title compound.

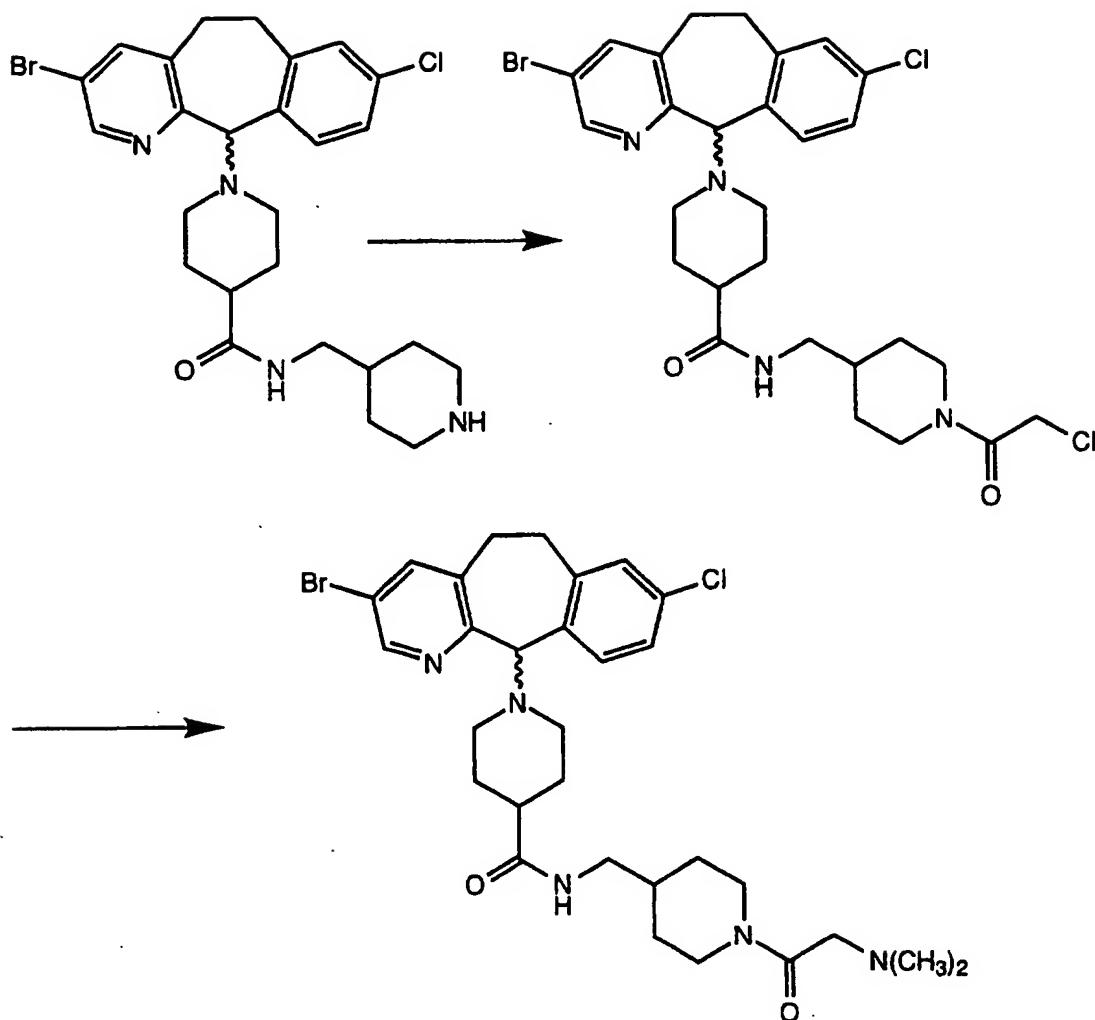
EXAMPLE 22



10 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) is reacted with an excess of acetic anhydride in methanol at 25°C for 24h to give the title compound.

15

EXAMPLE 23

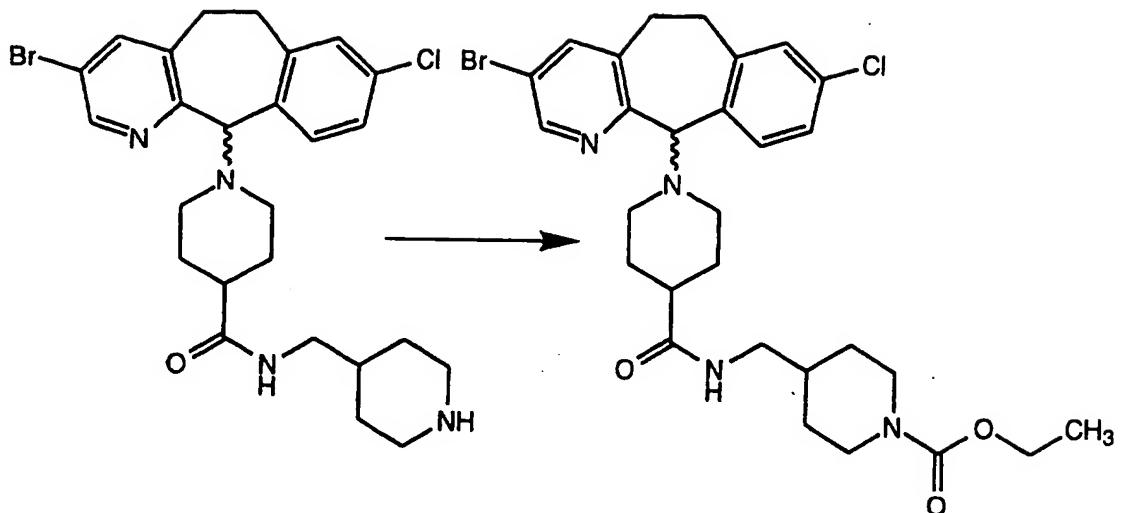


1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared

5 as described in Example 8, Procedures 1 or 2, Step B above) is reacted with chloroacetyl chloride (1.1 equivalents) and triethylamine (2 equivalents) in dichloromethane to give the intermediate chloroacetate. The latter is reacted with an excess of dimethylamine in the presence of sodium carbonate in DMF at 25°C to give the title compound.

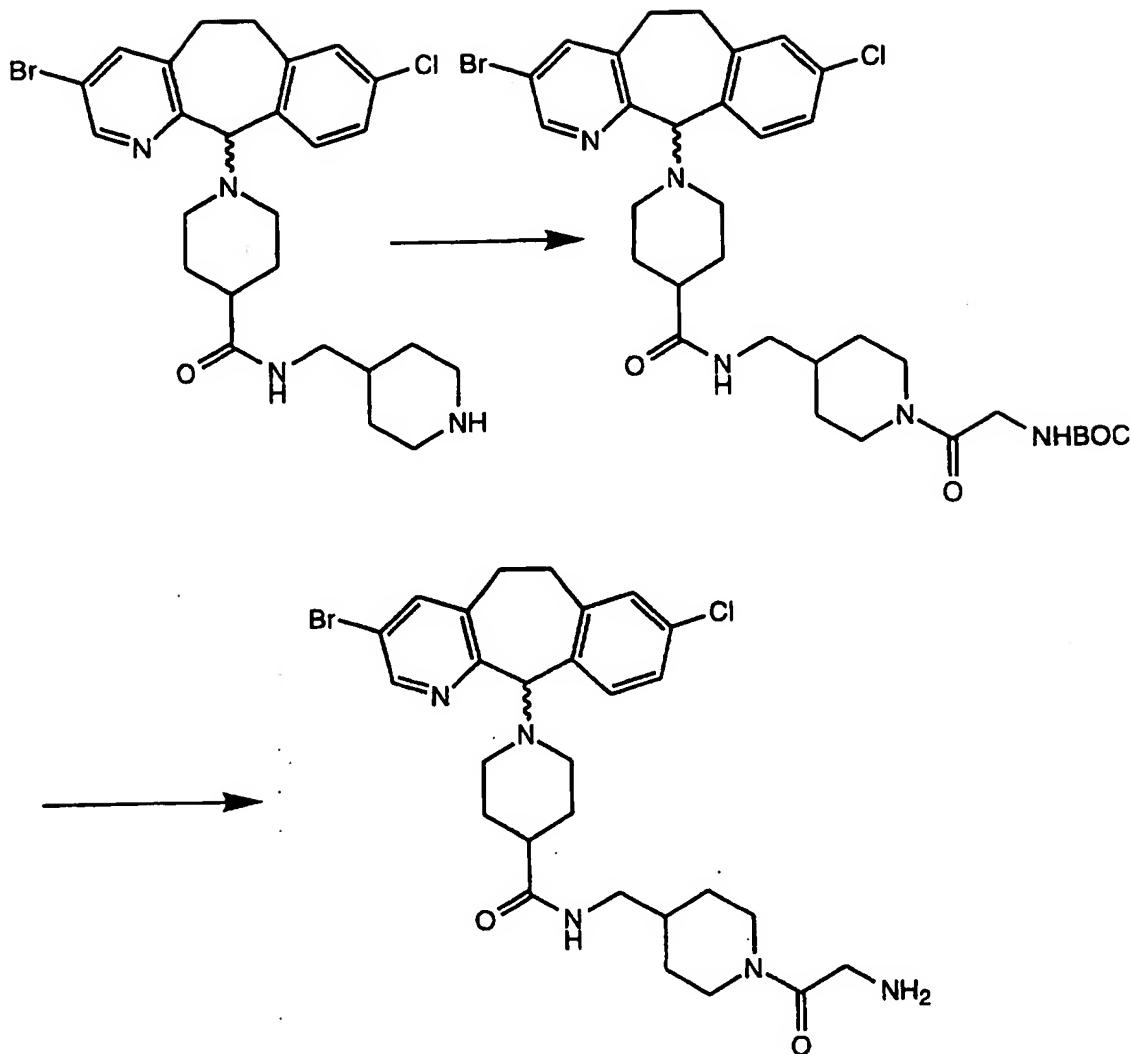
10

EXAMPLE 24



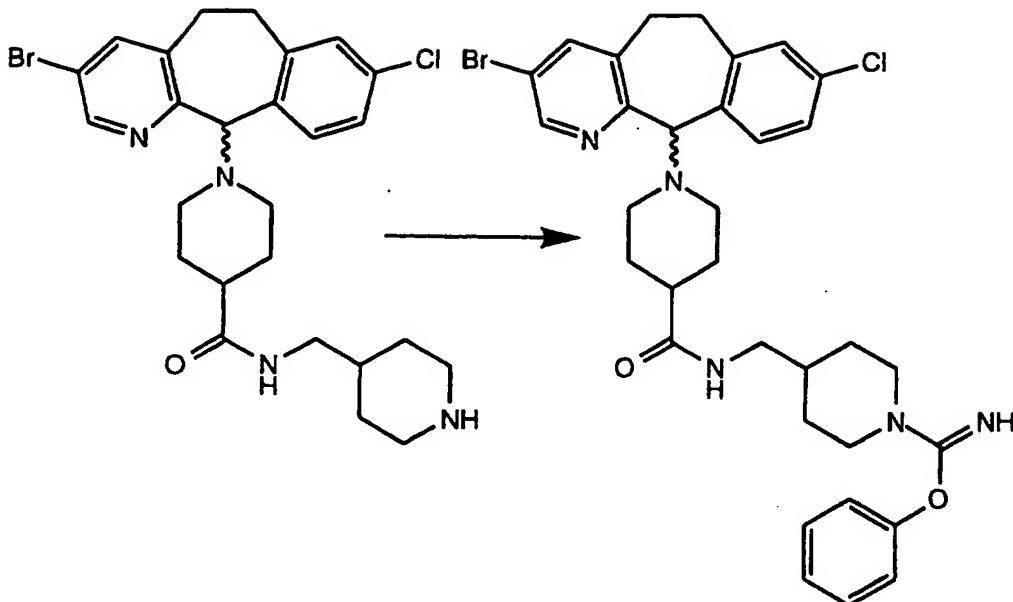
1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) is reacted with 5 ethylchloroformate (1.1 equivalents) in anhydrous dichloromethane at 25°C for 24h to give the title compound.

EXAMPLE 25



1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) is reacted with N-(*tert*-butoxycarbonyl)glycine (1.3 equivalents), DEC.HCl (1.3 equivalents), HOBT (1.3 equivalents) and N-methylmorpholine (1.3 equivalents) in anhydrous DMF at 25°C for 24h to give the N-BOC intermediate. The latter is dissolved in methanol and reacted with 10% concentrated sulfuric acid in dioxane at 25°C for 2h to give after basification and chromatography on silica gel, the title compound.

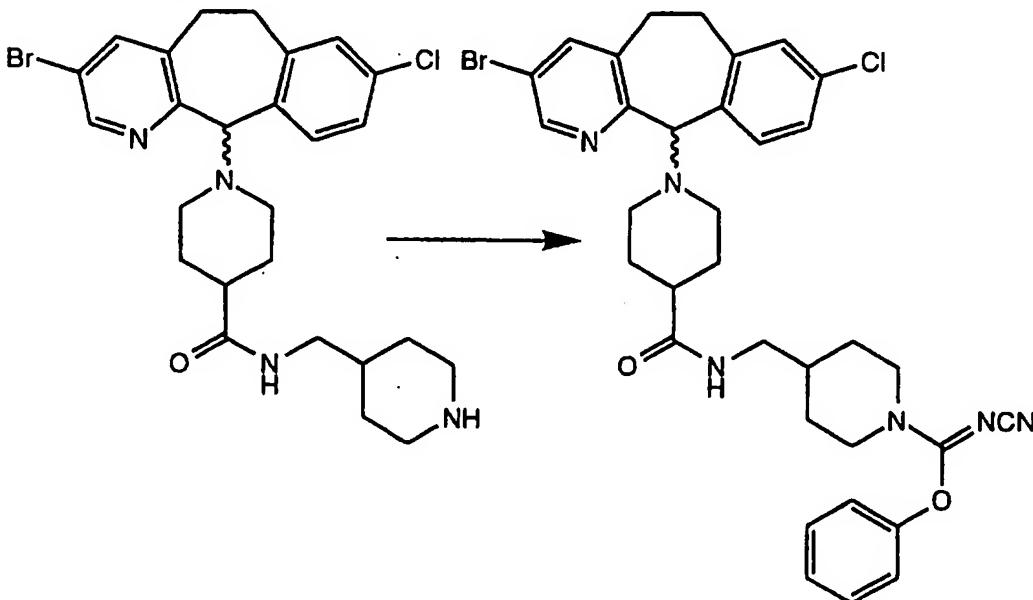
EXAMPLE 26



1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) in

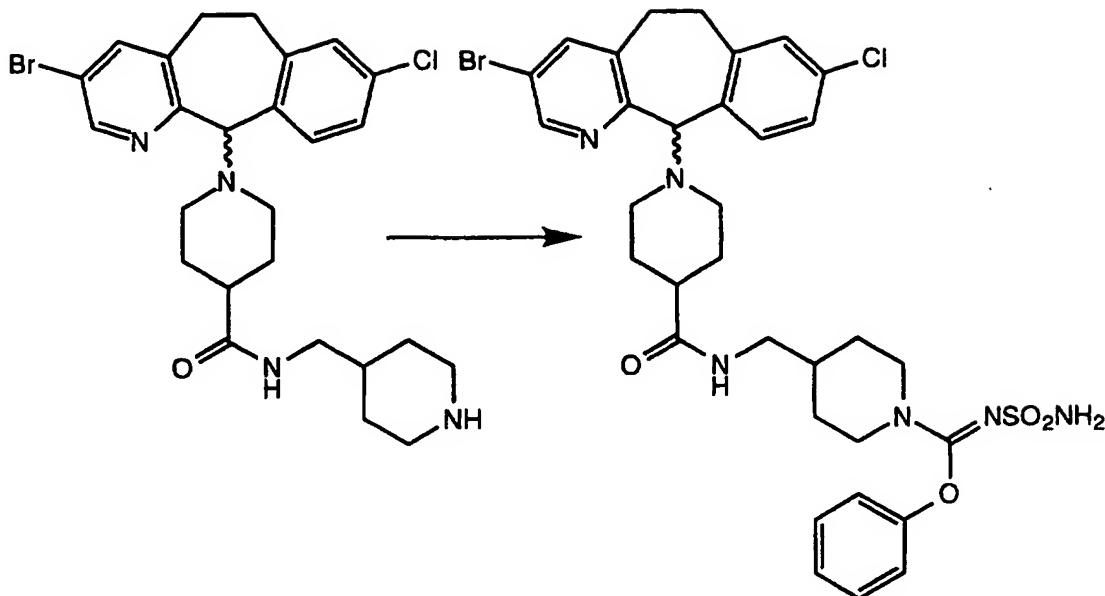
5 dichloromethane is reacted with phenyl cyanate (2 equivalents) and diisopropylethylamine at 25°C for 15 minutes to give the title compound.

EXAMPLE 27



10 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) and diphenylcyanocarbonimidate (1.2 equivalents) are dissolved in 2-propanol and the mixture is heated at 80°C for 24h to give the title compound.

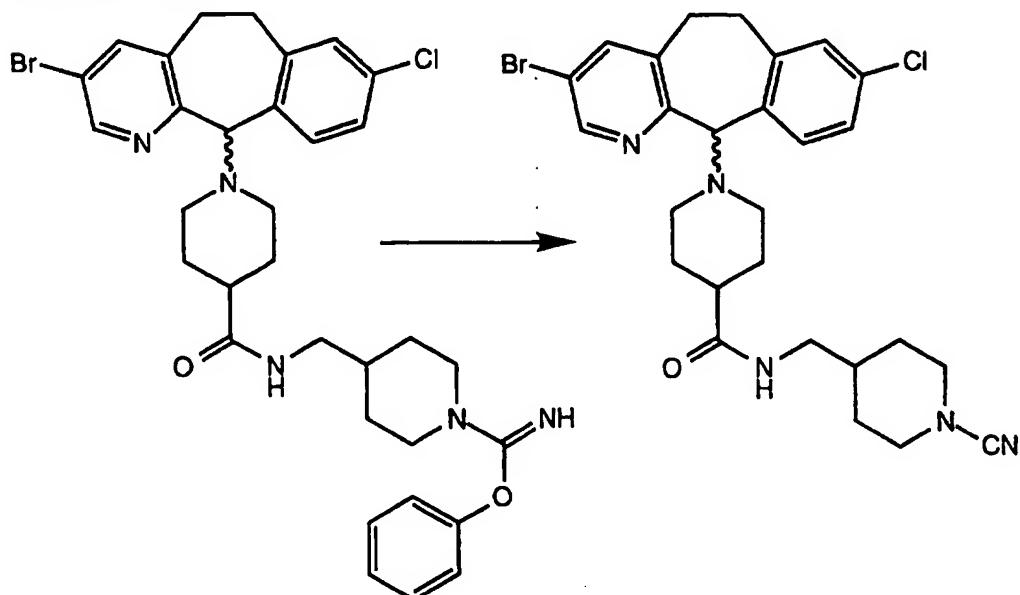
EXAMPLE 28



5 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) and diphenylsulfamoylcarbonimidate (1.2 equivalents) [prepared as described in: M. Haake and B. Schummelfeder, *Synthesis*, 753-758 (1991)] are dissolved in 2-propanol and the mixture is heated at 80°C for 24h to give the title compound.

10

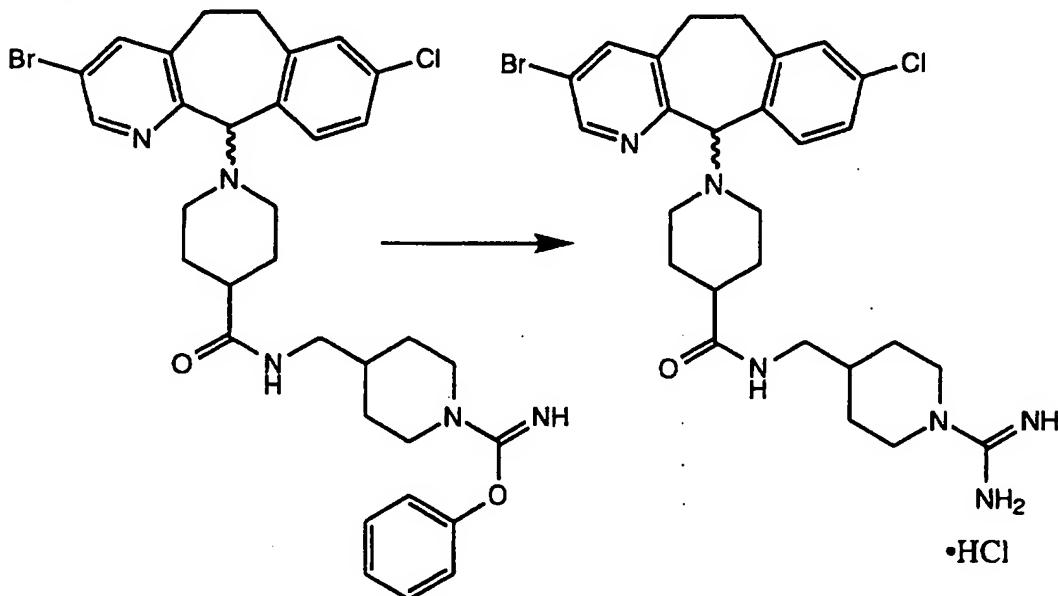
EXAMPLE 29



The phenoxyimide (1 equivalent) (prepared as described in Example 26 above) is dissolved in anhydrous THF. A 60% sodium hydride dispersion in oil (4 equivalents) is added and the mixture is stirred at 25°C for 2h. The mixture is diluted with dichloromethane and washed with 1N sodium hydroxide.

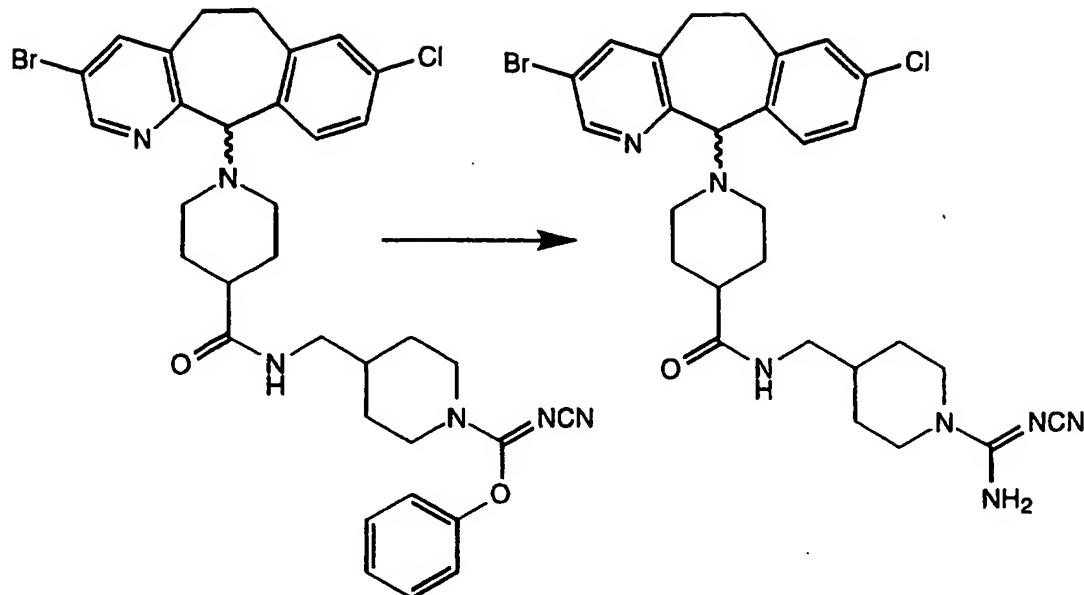
5 Chromatography on silica gel affords the title compound.

EXAMPLE 30



10 The phenoxyimide (1 equivalent) (prepared as described in Example 26 above) is dissolved in concentrated ammonium hydroxide and ammonium chloride (1 equivalent) is added. The mixture is heated in a sealed tube at 90°C to give the title compound.

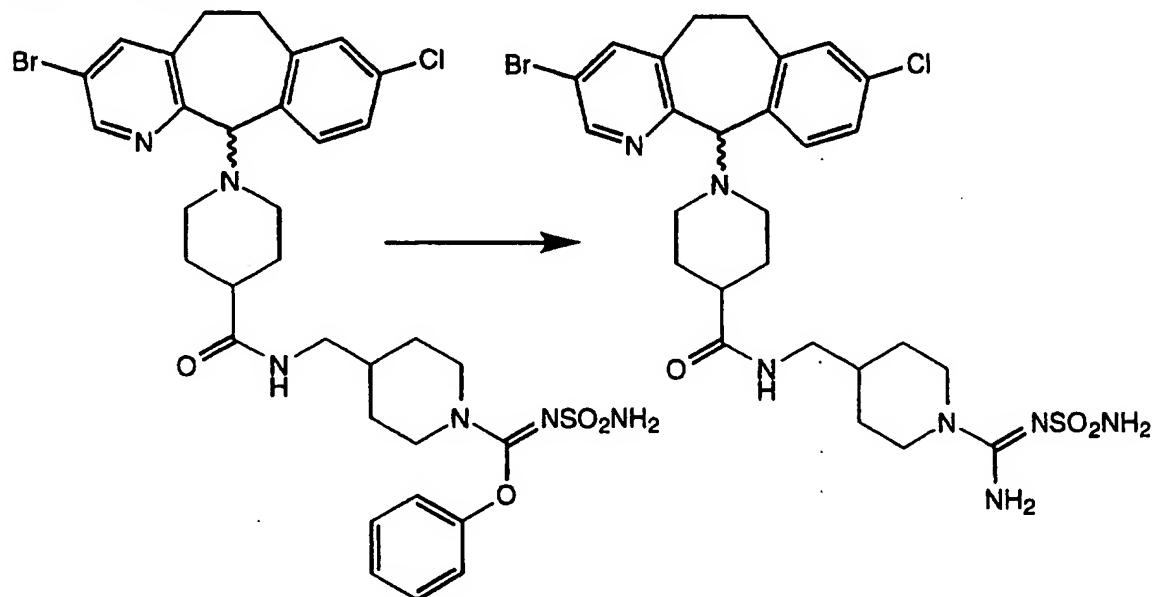
EXAMPLE 31



The N-cyanophenoxyimide (1 equivalent) (prepared as described in Example 27 above) is dissolved in concentrated ammonium hydroxide and the mixture is stirred at 25°C for 24h to give the title compound.

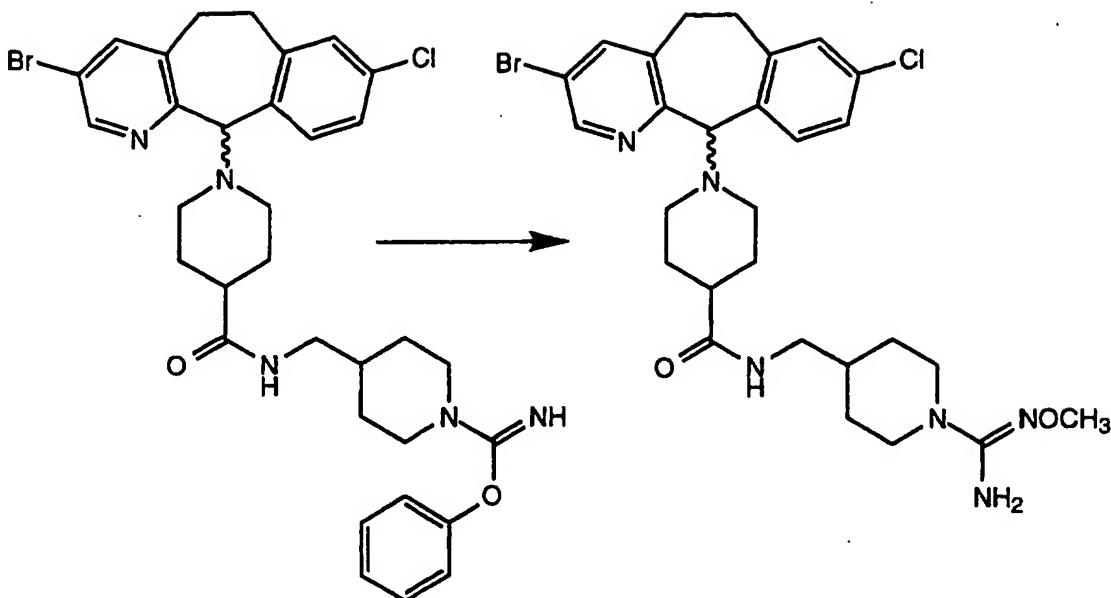
5

EXAMPLE 32



The N-sulfamoylphenoxyimide (1 equivalent) (prepared as described in Example 28 above) is dissolved in concentrated ammonium hydroxide and the mixture is stirred at 25°C for 24h to give the title compound.

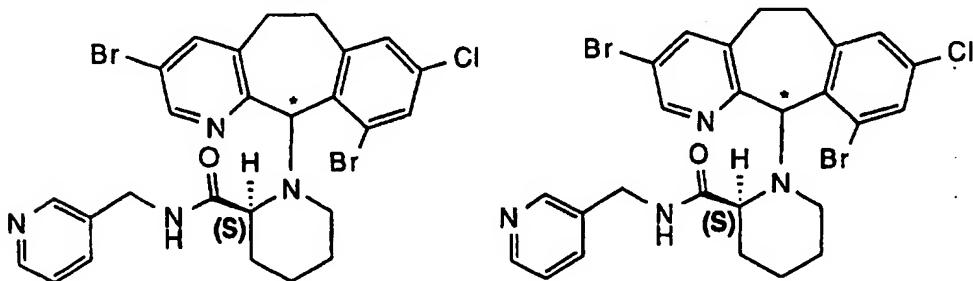
EXAMPLE 33



The phenoxyimide (1 equivalent) (prepared as described in Example 26 above) is dissolved in methanol. An aqueous solution of methoxylamine (1 equivalent) [prepared by dissolving methoxylamine hydrochloride (1 equivalent) in 50% (w/v) sodium hydroxide (1 equivalent)] is added and the mixture is stirred at 25°C to give the title compound.

EXAMPLE 34

Using the method of Example 14 except that 3,10-dibromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is substituted for 3-bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, the following two compounds are obtained:



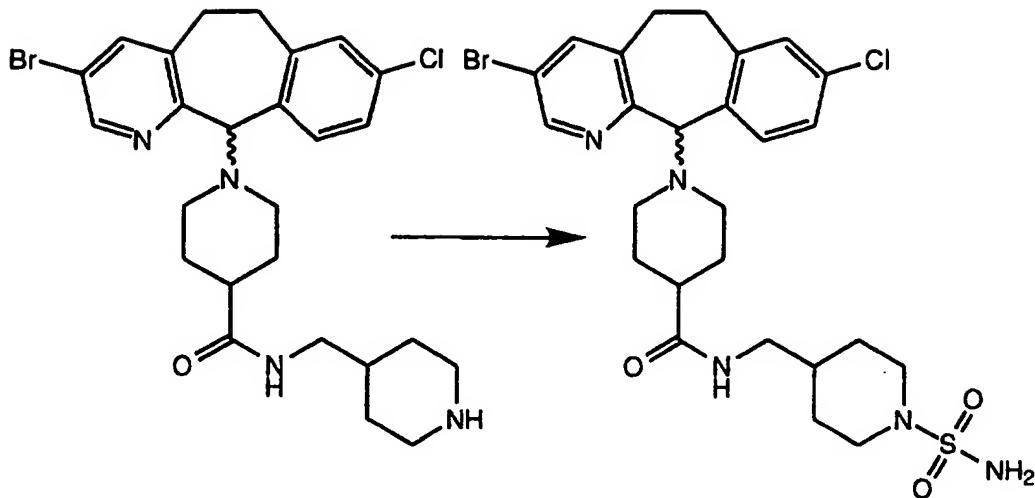
Isomer C3 amide

15 $MH^+ = 605$
 FPT $IC_{50} = 0.3 \mu M$

Isomer D3 amide

$MH^+ = 605$
 FPT $IC_{50} = 0.0042 \mu M$

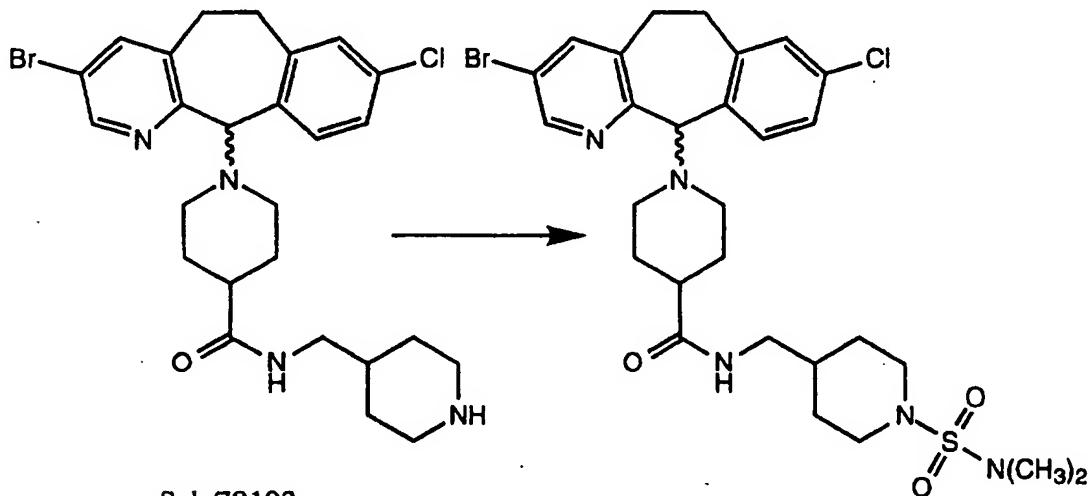
EXAMPLE 35



1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) and sulfamide (10 equivalents) are added to water and the mixture is stirred under reflux at 100°C for 43h to give the title compound.

5

EXAMPLE 36

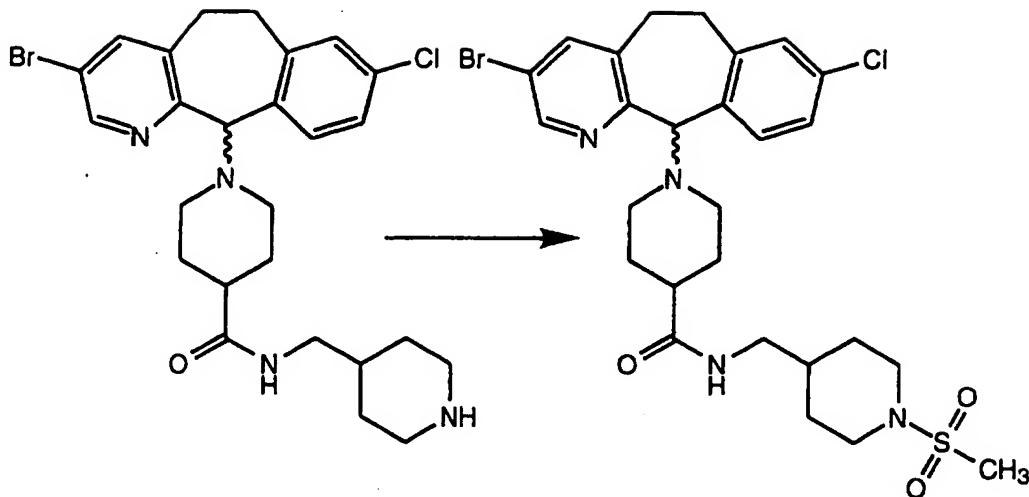


10 Sch 78193

1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) in dichloromethane is reacted with dimethylsulfamoyl chloride (1.1 equivalents) in the presence of triethylamine (2 equivalents) at from 0°C to 25°C to give the title compound.

15

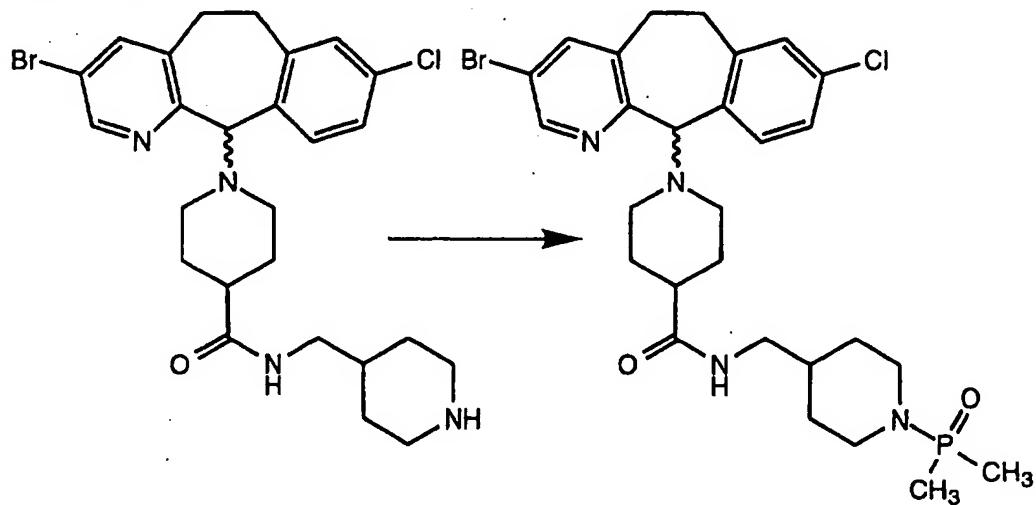
EXAMPLE 37



1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) in

5 dichloromethane is reacted with methanesulfonyl chloride (1.1 equivalents) in the presence of triethylamine (2 equivalents) at 25°C to give the title compound.

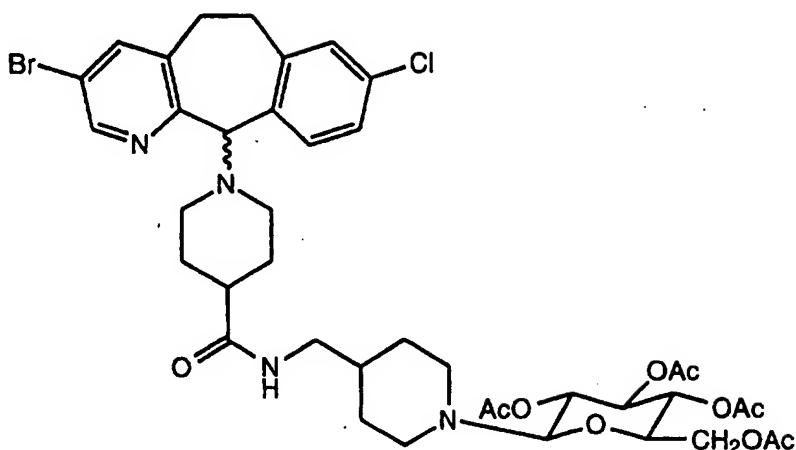
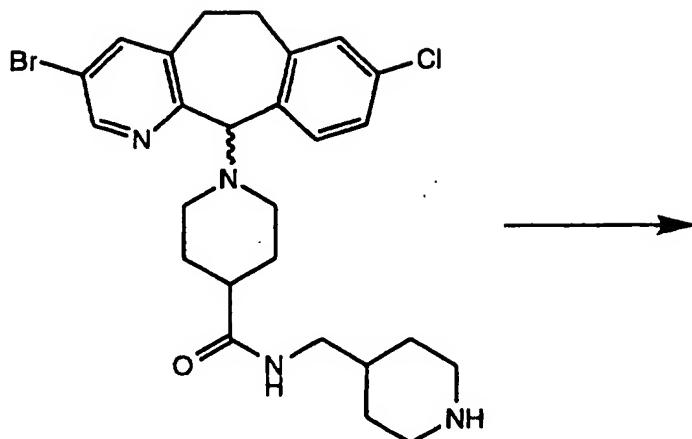
10 EXAMPLE 38



1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) in DMF is

15 reacted with dimethylphosphinic chloride (1.1 equivalents) and sodium carbonate at 25°C to give the title compound.

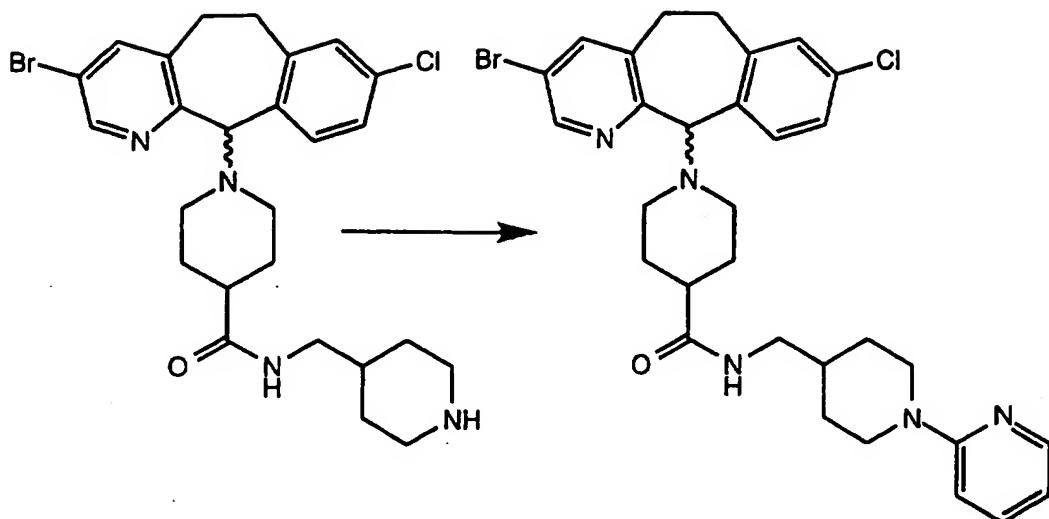
EXAMPLE 39



1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) in DMF is

5 reacted with tetra-O-acetyl-D-glucopyranosyl bromide (1.1 equivalents) in the presence of sodium carbonate to give the title compound.

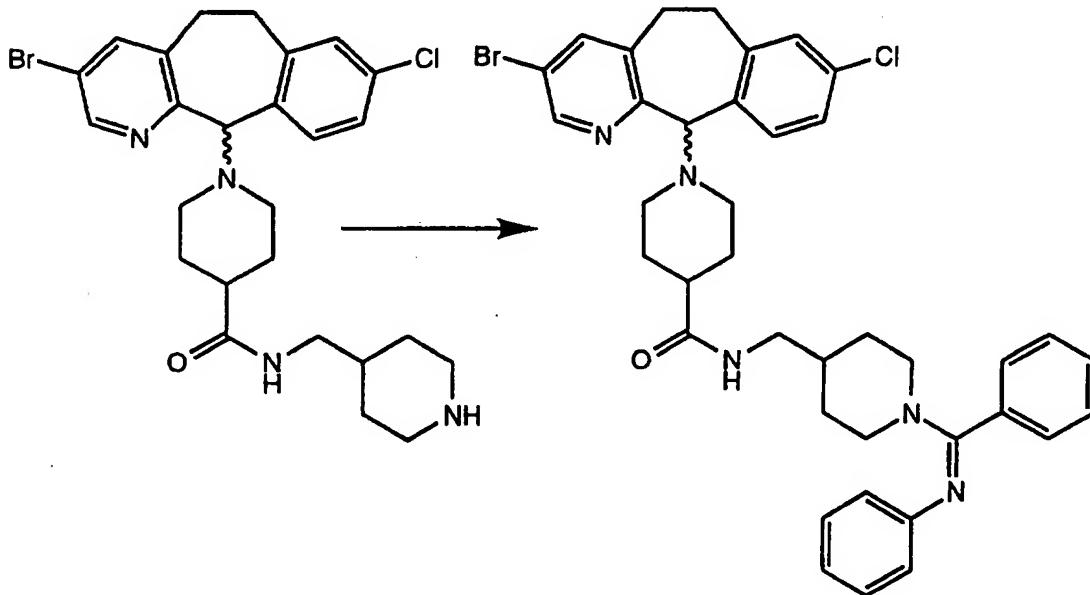
EXAMPLE 40



1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8, Procedures 1 or 2, Step B above) in DMF is

5 reacted with 2-chloropyridine (1.1 equivalents) in the presence of sodium carbonate to give the title compound.

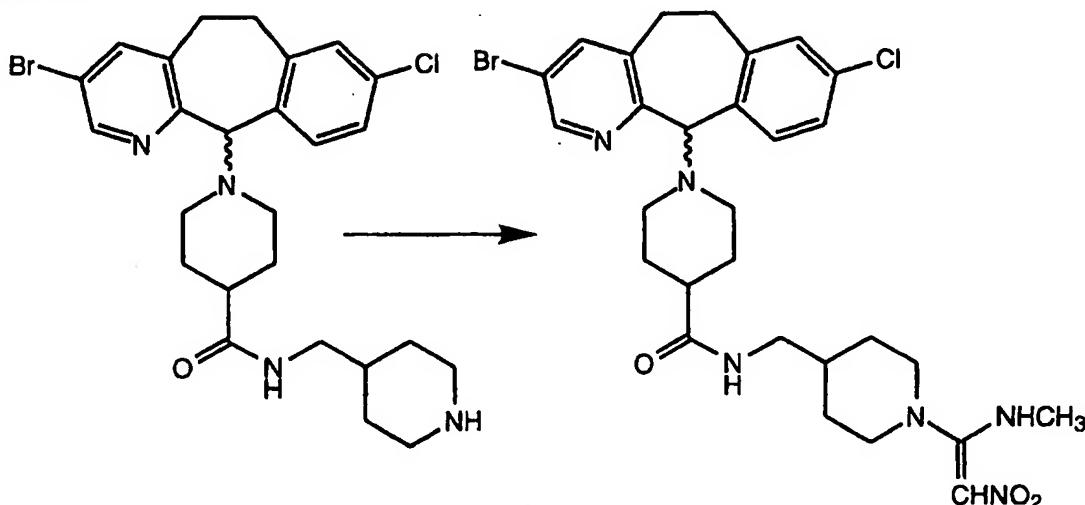
EXAMPLE 41



10 Benzaldehyde is converted into the chloroimide (as described in: A. C. Honz and E. C. Wagner, Org. Syn. Coll. Vol. 4, 383-386 (1963) (1.1 equivalents) and this is reacted with 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8,

Procedures 1 or 2, Step B above) in pyridine at reflux temperature to give the title compound.

Example 42



5

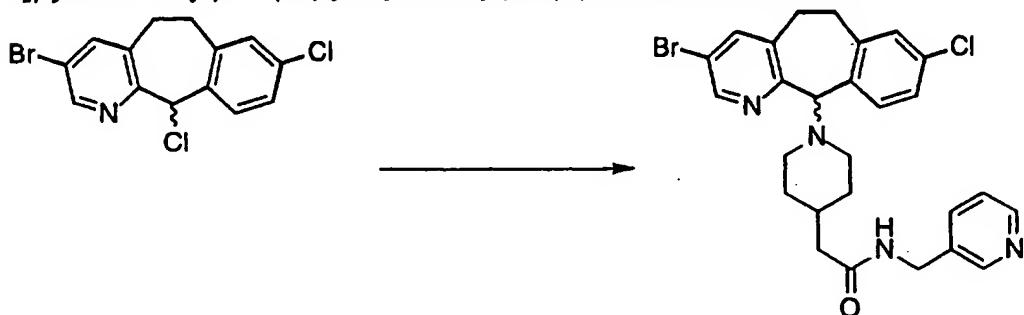
Copper(I)chloride (1 equivalent) is dissolved in anhydrous acetonitrile. To this solution, a solution of 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(4-piperidinylmethyl)-4-piperidinecarboxamide (1 equivalent) (prepared as described in Example 8,

10 Procedures 1 or 2, Step B above), 1-methylthio-1-methylamino-2-nitroethene (1 equivalent) (prepared as described in Canadian Patent 1,178,289 (1984)) and triethylamine in anhydrous acetonitrile is added dropwise over 10 minutes with stirring. The solid is filtered off. The volume is reduced and dichloromethane is added. The mixture is washed with aqueous sodium

15 bicarbonate and the dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The residue is purified on silica gel to give the title compound.

Example 43. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-

b]pyridin-11-yl)-N-(3-pyridylmethyl)-4-piperidineacetamide



3-Bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (0.317g, 0.924mmoles) is dissolved in anhydrous THF (4.6ml). N-(3-

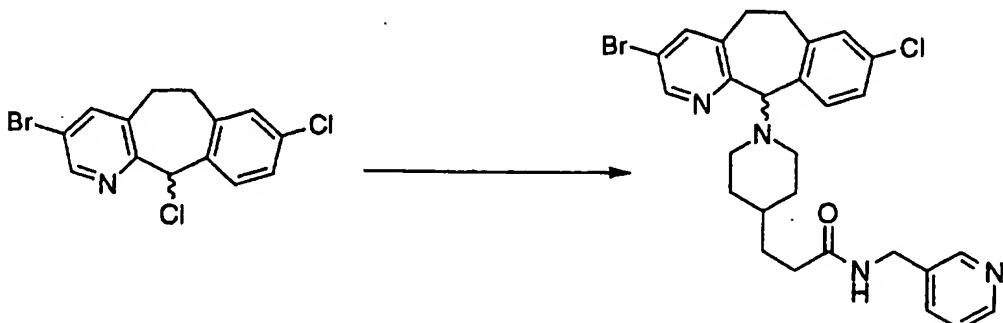
pyridylmethyl)-4-piperidineacetamide (prepared as described in Preparative Example 7, Step B) (0.2803g, 1.2mmoles) and triethylamine (0.386ml, 2.77mmoles) in anhydrous dichloromethane (5ml) are added and the mixture is stirred at 25°C for 18h. The solution is diluted with dichloromethane and

5 washed with 1N NaOH, dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on silica gel using 4% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.219g, 44%), SIMS: m/z 539 (MH⁺), FPT INH 43% @ 0.22μM.

10

		δ_C (CDCl ₃)
Tricyclic:	CH ₂ :	30.3, 30.5
	CH:	79.5, 126.1, 130.5, 132.4, 141.1, 146.9
	C:	120.2, 126.4, 134.1, 135.5, 136.4, 143.5, 154.0
Piperidine:	CH ₂ :	41.0, 46.8, 47.0, 50.9, 50.9
	CH:	33.5
	C:	172.0
Pyridine	CH ₂ :	43.6
substituent:	CH:	123.7, 135.7, 148.9, 149.1
	C:	133.8

Example 44. 1-(3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridylmethyl)-4-piperidinepropanamide



15 3-Bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (0.317g, 0.924mmoles) is dissolved in anhydrous THF (5ml). N-(3-pyridylmethyl)-4-piperidinepropanamide (prepared as described in Preparative Example 8, Step C) (0.2972g, 1.2mmoles) and triethylamine (0.386ml, 2.77mmoles) in anhydrous dichloromethane (20ml) are added and the mixture is stirred at 25°C for 20h. The solution is diluted with

20 dichloromethane and washed with 1N NaOH, dried over magnesium sulfate,

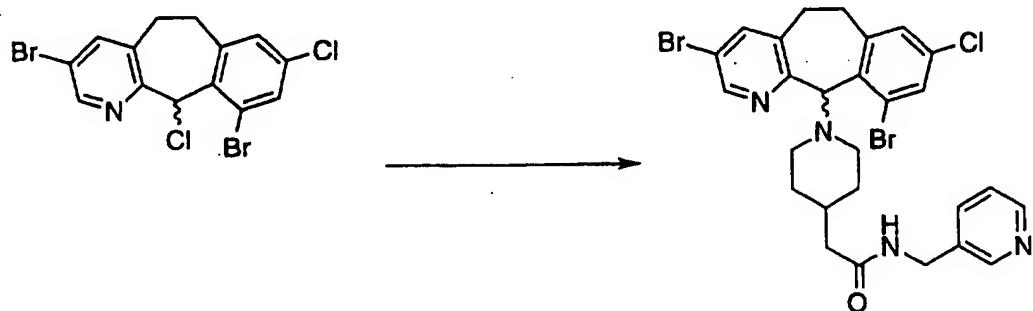
filtered and evaporated to dryness. The product is chromatographed on silica gel using 2.5% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.3022g, 59%), ESIMS: m/z 553.2 (MH⁺), FPT INH 39% @ 0.35μM.

5

δ_c (CDCl ₃)		
Tricyclic:	CH ₂ :	30.3, 30.5
	CH:	79.6, 126.0, 130.5, 132.3, 141.1, 146.8
	C:	119.6, 133.7, 136.6, 136.6, 140.6, 157.1
Piperidine:	CH ₂ :	32.1, 32.4, 32.4, 34.0, 52.0, 52.3
	CH:	35.6
	C:	173.2
Pyridine substituent:	CH ₂ :	41.0
	CH:	123.6, 136.6, 148.9, 149.2
	C:	134.2

Example 45. 1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridylmethyl)-4-piperidineacetamide

10

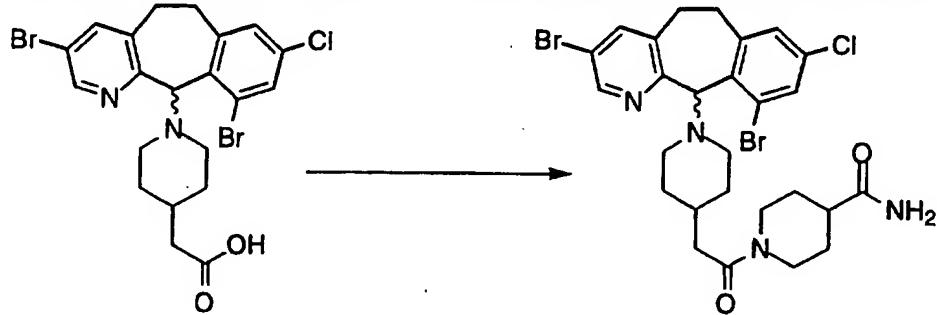


3,10-Dibromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (prepared as described in Preparative Example 6, Step F) (0.2426g, 0.575mmoles) is dissolved in anhydrous THF (2.86ml). N-(3-pyridylmethyl)-4-piperidineacetamide (prepared as described in Preparative Example 7, Step B) (0.175g, 0.748mmoles) and triethylamine (0.24ml, 1.725mmoles) in anhydrous THF (5ml) are added and the mixture is stirred at 25°C for 138h. The solution is evaporated to dryness and the residue is dissolved in dichloromethane and washed with 1N NaOH, dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on silica gel using 5% (10% conc. ammonium hydroxide in

methanol)-dichloromethane as the eluant to give the title compound (0.021g, 6%), ESIMS: m/z 617.2 (MH⁺), FPT IC₅₀ = 0.042μM.

δ_c (CDCl ₃)			
Tricyclic:	CH ₂ :	32.4, 32.4	
	CH:	75.6, 129.6, 130.7, 141.6, 147.2	
	C:	119.9, 126.2, 133.8, 136.2, 136.2, 143.2, 155.0	
Piperidine:	CH ₂ :	29.9, 31.2, 41.0, 51.0, 51.5	
	CH:	33.4	
	C:	171.9	
Pyridine substituent:	CH ₂ :	43.6	
	CH:	123.7, 135.7, 148.9, 149.1	
	C:	134.1	

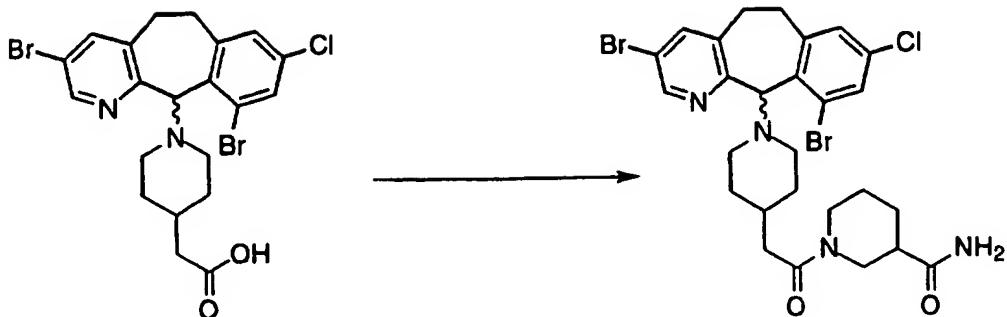
5 Example 46. 4-Carboxamido-1-[1-(8-chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetyl]piperidine



10 1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetic acid (0.5287g, 1mmole) (prepared as described in Preparative Example 10, Step B), isonipecotamide (0.1666g, 1.3mmoles), DEC.HCl (0.2492g, 1.3mmoles), HOBT (0.1757g, 1.3mmoles) and NMM (0.1315g, 1.3mmoles) are dissolved in anhydrous DMF (10ml) and the mixture is stirred at 25°C under argon for 24h. The solution is evaporated to dryness and the residue is dissolved in dichloromethane, washed with 1N NaOH, dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on silica gel using 0.75% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound.

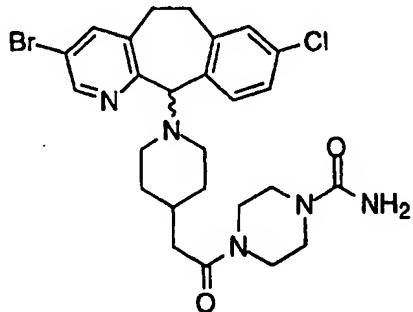
15 20

Example 47. 3-Carboxamido-1-[1-(8-chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetyl]piperidine

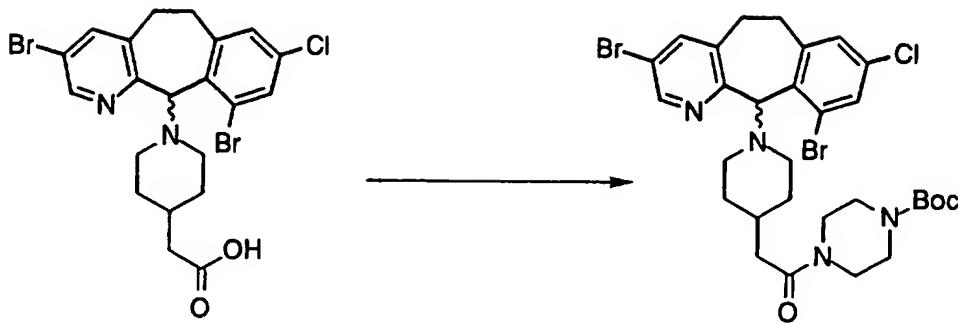


1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetic acid (0.5287g, 1mmole) (prepared as
 5 described in Preparative Example 10, Step B) and nipecotamide (0.1666g, 1.3mmoles), DEC.HCl (0.2492g, 1.3mmoles), HOBT (0.1757g, 1.3mmoles) and NMM (0.1315g, 1.3mmoles) are dissolved in anhydrous DMF (10ml) and the mixture is stirred at 25°C under argon for 24h. The solution is evaporated to dryness and the residue is dissolved in dichloromethane, washed with 1N
 10 NaOH, dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on silica gel using 0.75% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound.

15 Example 48. 4-[1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetyl]-1-piperazinecarboxamide



Step A. 4-[1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetyl]-1-N-tert-butoxycarbonylpiperazine
 20



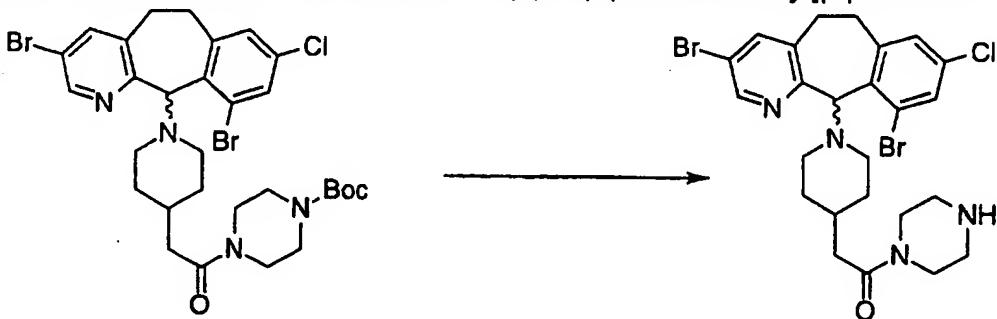
1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetic acid (0.5287g, 1mmole) (prepared as described in Preparative Example 10, Step B) and 1-N-*tert*-

5 butoxycarbonylpiperazine (0.1667g, 1.3mmoles), DEC.HCl (0.2492g, 1.3mmoles), HOBT (0.1757g, 1.3mmoles) and NMM (0.1315g, 1.3mmoles) are dissolved in anhydrous DMF (10ml) and the mixture is stirred at 25°C under argon for 24h. The solution is evaporated to dryness and the residue is dissolved in dichloromethane, washed with 1N NaOH, dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on silica gel using 0.75% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound.

10

Step B. 1-[1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-

15 benzo[5,6]cyclohepta[1,2-b] pyridin-11-yl)-4-piperidineacetyl]piperazine

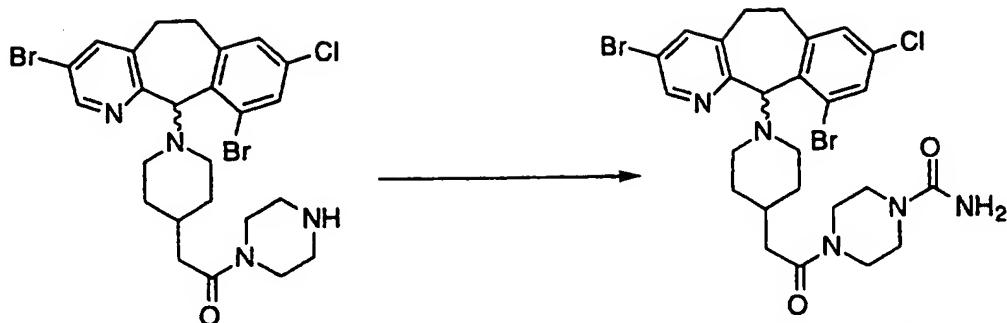


4-[1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetyl]-1-N-*tert*-butoxycarbonylpiperazine (prepared as described in Step A above) is converted into 1-[1-(8-Chloro-

20 3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetyl]piperazine by essentially the same procedure as described in Example 8, Procedure 2, Step B.

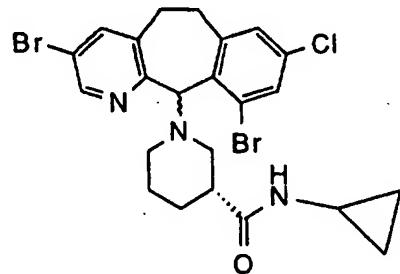
Step C. 4-[1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetyl]-1-piperazinecarboxamide

25



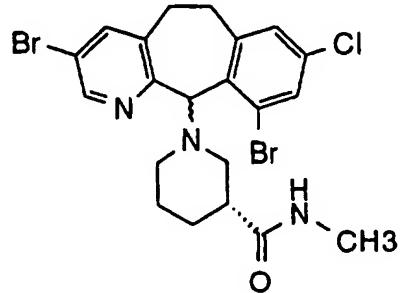
1-[1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetyl]piperazine (prepared as described in Step B above) is converted into 4-[1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetyl]-1-piperazinecarboxamide by essentially the same procedure as described in Example 8, Procedure 2, Step C above.

Example 49. N-cyclopropyl-1-(3,10-dibromo-8-chloro-6,11-dihydro-5H-10 benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-3-piperidinecarboxamide



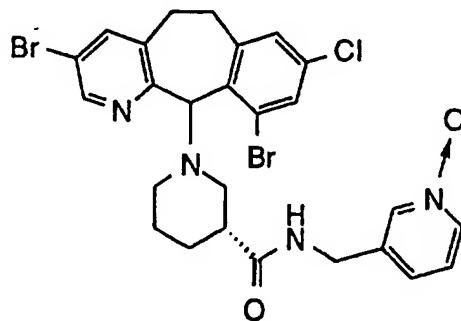
Following the method of Example 10, Procedure 1, except that (a) the compound 3,10-dibromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is substituted for 3-bromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine in Step A, and (b) cyclopropyl amine is substituted for 3-aminomethylpyridine in Step C, the title compound is obtained. FABMS (MH⁺) = 554. FPT IC₅₀ = 0.58 uM.

Example 50. 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-20 benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-methyl-3-piperidinecarboxamide



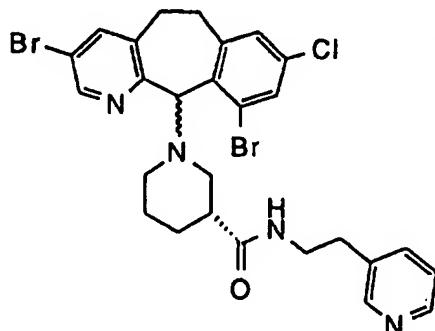
Following the method of Example 10, Procedure 1, except that (a) the compound 3,10-dibromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is substituted for 3-bromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine in Step A, and (b) 5 methylamine is substituted for 3-aminomethylpyridine in Step C, the title compound is obtained. FABMS (MH⁺) = 528. FPT IC₅₀ = 0.96 uM.

10 Example 51. 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-(3-pyridinylmethyl)-3-piperidinecarboxamide N1-oxide (Isomer B)



Following the method of Example 10, Procedure 1, except that (a) the compound 3,10-dibromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is substituted for 3-bromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine in Step A, and (b) 15 3-aminomethylpyridine-N-oxide is substituted for 3-aminomethylpyridine in Step C, the title compound is obtained. FABMS (MH⁺) = 619. FPT IC₅₀ = 0.1 uM.

20 Example 52. 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-[2-(3-pyridinyl)ethyl]-3-piperidinecarboxamide



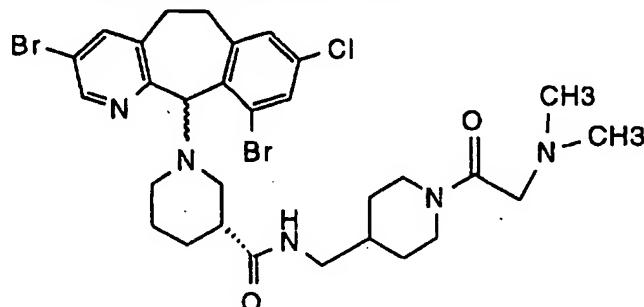
25 Following the method of example 10, procedure 1, except that (a) the compound 3,10-dibromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is substituted for 3-bromo-8,10-dichloro-

6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine in Step A, and (b) 3-aminoethylpyridine is substituted for 3-aminomethylpyridine in Step C, the title compound is obtained. FABMS (MH^+) = 617.

FPT IC₅₀ = 0.081 μ M

5

Example 53. 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-[(1-[(dimethylamino)acetyl]-4-piperidinyl)methyl]-3-piperidinecarboxamide

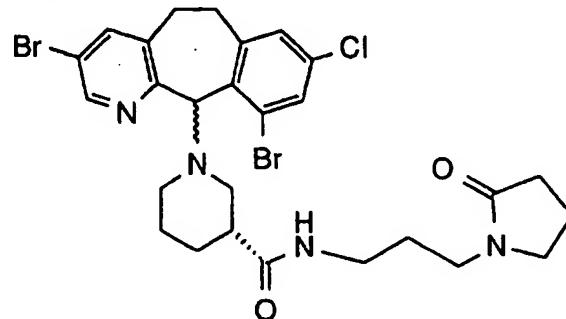


10

Following the method of Example 10, Procedure 1, except that (a) the compound 3,10-dibromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine is substituted for 3-bromo-8,10-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine in Step A, and (b) dimethylaminoacetyl-4-piperidinylmethyl-3-amine is substituted for 3-aminomethylpyridine in Step C, the title compound is obtained.

Example 54. 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-

20 **benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-N-[3-(2-oxo-1-pyrrolidinyl)propyl]-3-piperidinecarboxamide**



Following the method of Example 10, Procedure 1, except that (a) the compound 3,10-dibromo-8,10-dichloro-6,11-dihydro-5H-
benzo[5,6]cyclohepta[1,2-b]pyridine is substituted for 3-bromo-8,10-dichloro-
6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine in Step A, and (b)

3-aminopropylpyrrolidinone amine is substituted for 3-aminomethylpyridine in Step C, the title compound is obtained. FABMS (MH⁺) = 637.
FPT IC₅₀ = 0.1 μ M

5 **PREPARATION OF STARTING MATERIALS**

Starting materials useful in preparing the compounds of the present invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. The tricyclic compounds (3.0) and substituted piperidinyl compounds (7.0) used as starting materials are known 10 in the art and/or can be prepared using known methods, such as taught in U.S. Patents 5,089,496; 5,151,423; 4,454,143; 4,355,036; PCT /US94/11390 (WO95/10514); PCT/US94/11391 (WO 95/10515); PCT/US94/11392 (WO95/10516); Stanley R. Sandler and Wolf Karo, *Organic Functional Group Preparations*, 2nd Edition, Academic Press, Inc., San Diego, California, Vol. 1-15 3, (1983); in J. March, *Advanced Organic Chemistry, Reactions & Mechanisms, and Structure*, 3rd Edition, John Wiley & Sons, New York, 1346 pp. (1985); in G. R. Newkome (Ed.), *Pyrdine and its Derivatives*, John Wiley and Sons Inc., New York, N.Y., Vol. 1-5, (1984); A. J. Boulton and A. McKillop (Eds.), *Comprehensive Heterocyclic Chemistry*, Volume 2, Part 2A, Six 20 Membered Rings With One Nitrogen Atom, Pergamon Press, Elmsford, New York, (1960-1985); and Chia-Lin J. Wang and Mark A. Wuonola, *Recent Progress in the Synthesis and Reactions of Substituted Piperidines. A Review*, *Organic Preparations and Procedures International* Vol 24, p. 585, (1992). The starting materials may also be prepared as taught in copending U.S. 25 Application Serial No. 08/410,187 filed March 24, 1995, copending U.S. Application Serial No. 08/577,951 filed December 22, 1995, and copending U.S. Application Serial No. 08/615,760 filed March 13, 1996; the disclosures being incorporated herein by reference. Alternative mechanistic pathways 30 and analogous structures within the scope of the invention may be apparent to those skilled in the art.

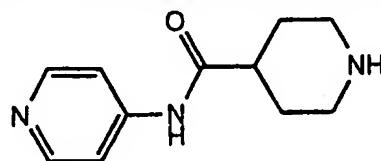
For example, piperidinyl compounds of formula (7.0), wherein T = -CO- or -CR³⁰R³¹- can be prepared by initially preparing a pyridine compound substituted with the requisite 2-, 3-, or 4- -(CH₂)_nCR³⁰R³¹Z or -(CH₂)_nCOZ moiety, together with any optional -R⁵, -R⁶, -R⁷ and/or -R⁸ moieties, as 35 described, in the references cited above. The 2-, 3- or 4-substituted pyridine compound can subsequently be reduced using conventional reduction procedures, such as catalytic hydrogenation, to give the desired piperidinyl

compound (7.0). One skilled in the art will appreciate that in cases where -R⁵, -R⁶, -R⁷, -R⁸ and/or Z moieties also contain reducible groups, it may be useful to utilize alternative methods.

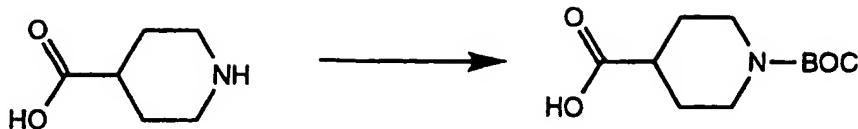
The sulfonylpiperidinyl compounds of formula (7.0), wherein T= -SO₂- can be prepared by reacting the appropriate 2-, 3-, or 4-hydroxy-N-blocked-piperidine with a suitable chlorinating agent such as thionyl chloride to obtain the 2-, 3-, or 4-chloro-N-blocked piperidine, using N-blocking groups such as benzyloxycarbonyl or tert-butoxycarbonyl. The 2-, 3-, or 4-chloro-N-blocked piperidine can then be reacted with sodium bisulfite to obtain the corresponding 2-, 3-, or 4-sulfonic acid N-blocked piperidine sodium salt. This salt is then reacted with an appropriate chlorinating agent such as phosphorus pentachloride or phosphorus oxychloride to obtain the corresponding 2-, 3- or 4-sulfonylchloride-N-blocked piperidine. This sulfonyl chloride is then reacted with the corresponding agent containing the desired Z group (i.e. amines, alkylating agents and the like) to obtain the desired sulfonylpiperidinyl (7.0).

The sulfoxylpiperidinyl wherein T= -SO- (with the proviso that Z is not -NR₄₀R₄₂) can be prepared by reacting the appropriate 2-, 3-, or 4-hydroxy-N-blocked-piperidine with a suitable chlorinating agent such as thionyl chloride to obtain the 2-, 3-, or 4-chloro-N-blocked piperidine, using N-blocking groups such as benzyloxycarbonyl or tert-butoxycarbonyl. The 2-, 3-, or 4-chloro-N-blocked piperidine can then be reacted with the corresponding substituted sulfide (i.e. arylsulfide, alkylsulfides and the like) to obtain the appropriate 2-, 3-, or 4-sulfide-N-blocked piperidine. This compound can then be reacted with an oxidizing agent such as meta-chloroperbenzoic acid to obtain the desired sulfoxylpiperidinyl (7.0).

PREPARATIVE EXAMPLE 1. 4-Piperidinyl-N-(4-pyridinyl)carboxamide



30 Step A:
1-N-(tert -Butoxycarbonyl)-4-piperidine carboxylic acid or 1-N-(tert -butoxycarbonyl)isonipecotic acid

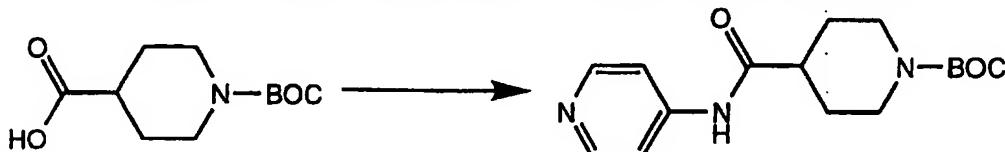


Isonipecotic acid (5g; 1 equivalent) is dissolved in water (50 ml) and a solution of di-*tert*-butyldicarbonate (8.62g; 1.02 equivalents) in THF (70 ml) is added with stirring. The mixture is stirred at 80°C for 2 h and then evaporated to dryness. The residue is partitioned between dichloromethane and brine and the dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (30 X 5cm) using 15% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (4.3109g; 49% yield), CIMS: m/z 230 (MH⁺).

5 with stirring. The mixture is stirred at 80°C for 2 h and then evaporated to dryness. The residue is partitioned between dichloromethane and brine and the dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (30 X 5cm) using 15% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (4.3109g; 49% yield), CIMS: m/z 230 (MH⁺).

10 Step B:

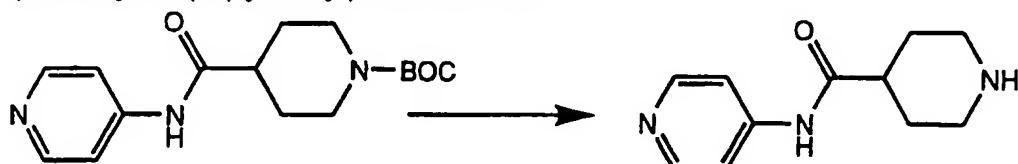
1-N-(*tert*-Butoxycarbonyl)-4-piperidinyl-N-(4-pyridinyl)carboxamide



15 1-N-(*tert*-Butoxycarbonyl)-4-piperidinyl-N-(4-pyridinyl)carboxamide (1.218; 1 equivalent) (prepared as described in Step A above), DEC (1.0184g; 1 equivalent), HOBT (0.7179g; 1 equivalent) and N-methylmorpholine (0.5841ml; 1 equivalent) are dissolved in anhydrous DMF (30 ml) and the mixture is stirred under argon at 25°C for 19 h. The solution is evaporated to dryness. The residue is taken up in dichloromethane and washed with water. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (60 X 2.5 cm) using 5% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.8142g; 50% yield), CIMS: m/z 306 (MH⁺).

20 Step C:

25 4-Piperidinyl-N-(4-pyridinyl)carboxamide

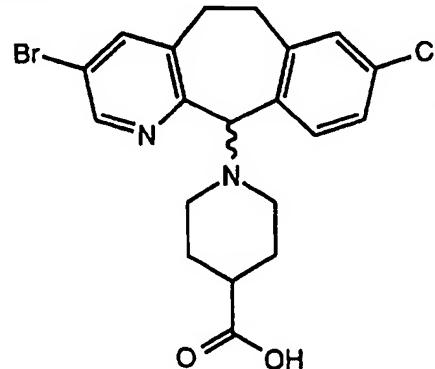


30 1-N-(*tert*-Butoxycarbonyl)-4-piperidinyl-N-(4-pyridinyl)carboxamide (1g; 1 equivalent) is dissolved in 10% (v/v) concentrated sulfuric acid in dioxane

(24.36ml) and the mixture is stirred at 25°C for 0.5 h. The mixture is poured into water (150 ml) and neutralized with Amberlite IRA401S(OH⁻) ion exchange resin (300ml). The resin is eluted with water (1500 ml) and the eluant is evaporated to give the title compound (0.4258g; 63% yield), CIMS: 5 m/z 206 (MH⁺).

PREPARATIVE EXAMPLE 2

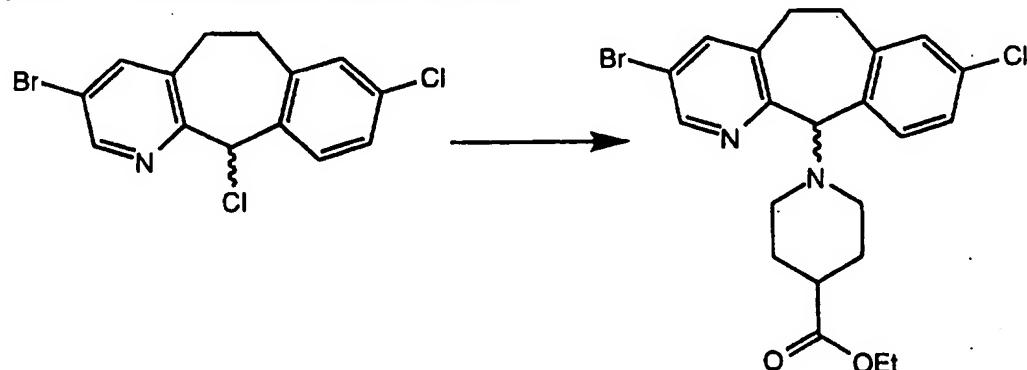
1-[3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-piperidinecarboxylate



10

Procedure 1, Step A:

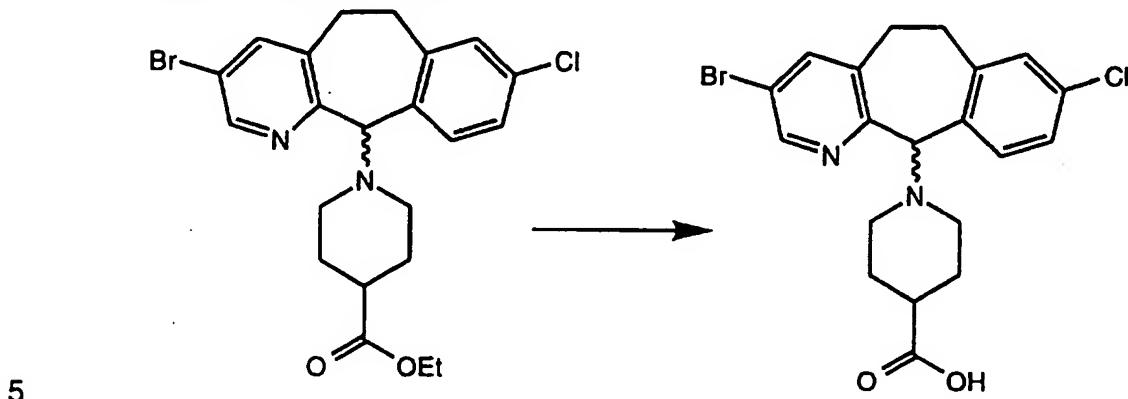
Ethyl 1-[3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-piperidinecarboxylate



15 3-Bromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (1g; 1 equivalent) and ethyl isonipeacetate (2.3735ml) (5 equivalents) are dissolved in dry THF (20ml) and the mixture was stirred at 25°C under argon for 19h. The solution is evaporated to dryness and the residue is taken up in dichloromethane and washed with 1.0N sodium hydroxide. The 20 dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel column (30X5cm) using 0.75% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (1.5134g; 100% yield), CIMS: m/z 463.15 (MH⁺).

Step B:

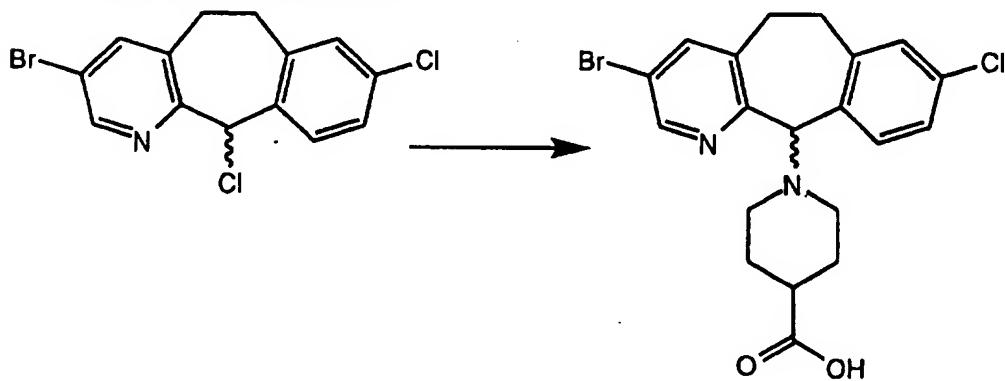
1-[3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-piperidinecarboxylate



15 Ethyl 1-[3-bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-piperidinecarboxylate (0.250g; 1 equivalent) (prepared as described in Step A above), is dissolved in ethanol (3ml) and dichloromethane (3ml) and 1.0M lithium hydroxide in water (1.3044ml; 2.42 equivalents) is added. The mixture is stirred at 50°C for 5h. 1.0N Hydrochloric acid (1.5169ml) (2.81 equivalents) is added and the solution is evaporated to dryness after stirring for 5 min. to give the title compound which is used without further purification.

15 Procedure 2:

1-[3-Bromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-4-piperidinecarboxylate

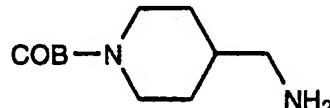


20 3-Bromo-8,11-Dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridine (prepared as described in Preparative Example 40, Step B in INO291K) (0.5g; 1 equivalent), isonipecotic acid (0.3978g; 2 equivalents) and 4-N-methylmorpholine (0.847ml; 5 equivalents) are dissolved in anhydrous DMF (9.6ml) and the mixture is heated at 80°C for 16.5h. The solution is evaporated

to dryness and the product is chromatographed on a silica gel column (60X2.5cm) using 10% ethyl acetate in hexane, followed by 1% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.2426g; 36% yield), CIMS: m.z 435.1
5 (MH⁺).

PREPARATIVE EXAMPLE 3

4-(Aminomethyl)-1-N-(*tert*-butoxycarbonyl)piperidine

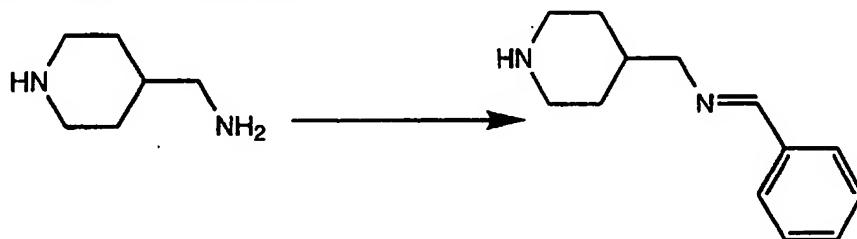


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Ref.: J. D. Prugh, L. A. Birchcough and M. S. Egbertson, Synthetic Communications, 22(16), 2357-2360 (1992).

Step A:

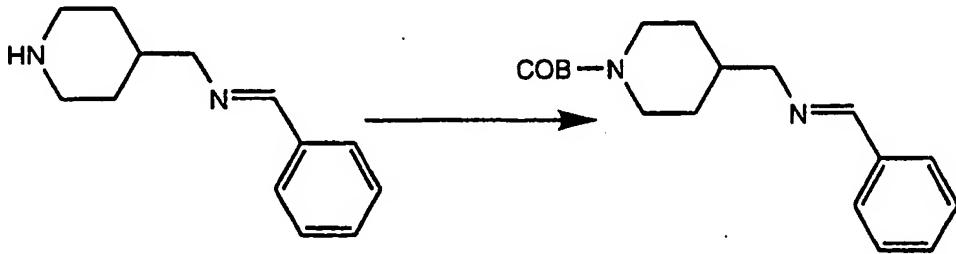
15 4-(Benzylideneaminomethyl)piperidine



20 4-Aminomethylpiperidine (11.4g) (1 equivalent) is dissolved in anhydrous toluene (125ml) and benzaldehyde (10.6g) (1 equivalent) is added. The mixture is heated at 120°C under reflux for 4h, using a Dean-Stark trap to remove water. The crude solution of the title compound is used directly in Step B below.

Step B:

1-N-(*tert*-Butoxycarbonyl)-4-(benzylideneaminomethyl)piperidine



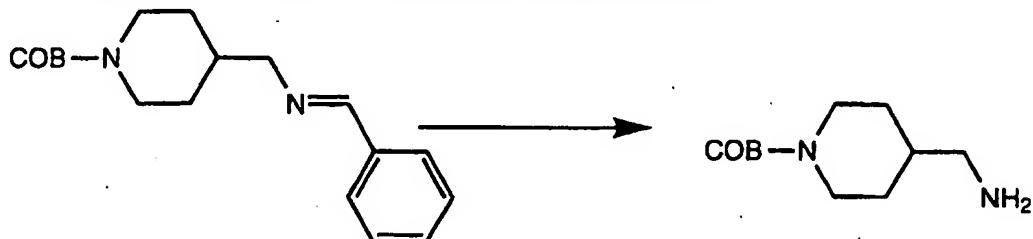
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4-(Benzylideneaminomethyl)piperidine in toluene (From Step A above) is treated with di-*tert*-butyldicarbonate (24g) (1.1 equivalents) in portions over

0.5h. The mixture is stirred at 25°C for 69h. The solution is evaporated to dryness to give the title compound which is used directly in Step C below.

Step C:

5 4-(Aminomethyl)-1-N-(*tert*-butoxycarbonyl)piperidine

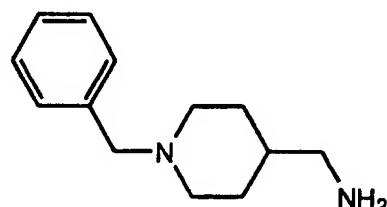


1-N-(*tert*-Butoxycarbonyl)-4-(benzylideneaminomethyl)piperidine (prepared as described in Step B above) is dissolved in 1.0N aqueous potassium hydrogen sulfate (220ml) and the mixture is stirred at 25°C for 4h. The solution

10 is extracted with ether (3X200ml) and the ether is discarded. The aqueous layer is adjusted to pH 12.5 using 50% aqueous sodium hydroxide and the solution is then saturated with solid sodium chloride and extracted with dichloromethane. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a 15 silica gel column (60 X 5cm) using 1% increasing to 7% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (9.82g; 46% yield), an oil, CIMS: m/z 215 (MH⁺).

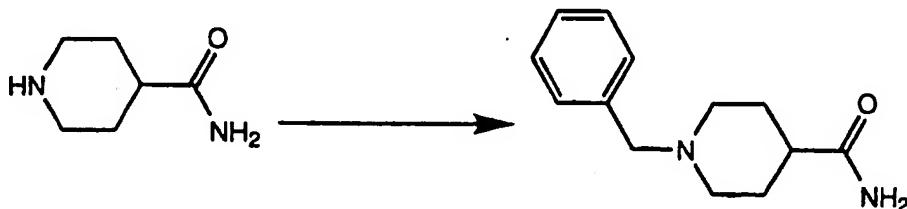
PREPARATIVE EXAMPLE 4 1-N-Benzyl-4-(aminomethyl)piperidine

20



Step A:

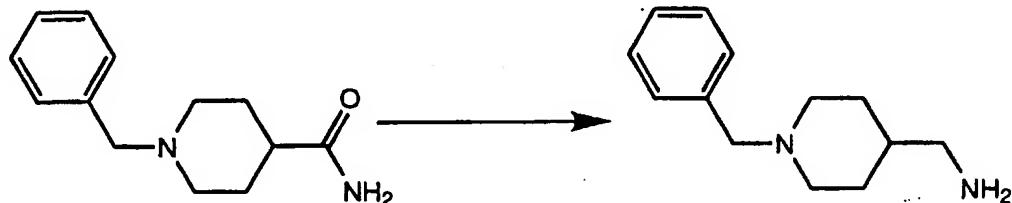
1-N-Benzyl-4-piperidinecarboxamide



25 4-Piperidinecarboxamide (5g; 1 equivalent) and triethylamine (16.3ml) (3 equivalents) are dissolved in anhydrous dichloromethane (30ml) and

anhydrous DMF (80ml). A solution of benzyl bromide (4.55ml) (0.98 equivalents) in anhydrous dichloromethane (10ml) is added dropwise over 10 min and the mixture is stirred at 25°C for 22h. The mixture is filtered and the filtrate is evaporated to dryness. The product is chromatographed on a silica 5 gel column (60X5cm) using dichloromethane (1 litre) and then 5% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (6.15g; 72% yield), CIMS: m/z 219.05 (MH⁺).

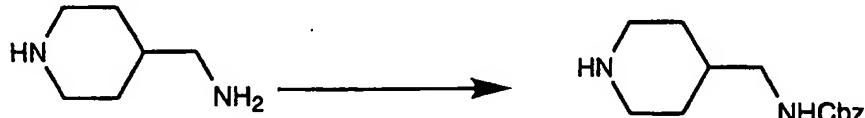
Step B:
10 1-N-Benzyl-4-(aminomethyl)piperidine



15 1-N-Benzyl-4-piperidinecarboxamide (1g; 1 equivalent) (prepared as described in Step A above) is dissolved in anhydrous THF (25ml). Lithium aluminum hydride (0.2173g) (1.25 equivalents) in anhydrous THF (5.726ml) is added dropwise over 0.5h and the mixture is heated under reflux under nitrogen for 20h. The mixture is cooled and diluted with dichloromethane (750ml) and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The 20 product is chromatographed on a silica gel column (60X2.5cm) using 2% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.5237g; 56% yield), FABMS: m/z 205.4 (MH⁺).

25 PREPARATIVE EXAMPLE 5

Step A:
4-(N-Benzylloxycarbonylaminomethyl)piperidine

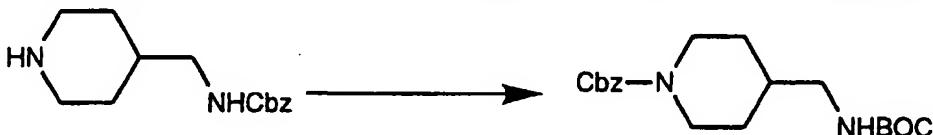


30 4-Aminomethylpiperidine (1g; 1 equivalent) and DMAP (0.054g; 0.05 equivalents) are dissolved in anhydrous dichloromethane (40 ml). N-Benzylloxycarbonylimidazole (1.7709g; 1 equivalent) [prepared as described in: S. K. Sharma, M. J. Miller and S. M. Payne, J. Med. Chem., 32, 357-367

(1989)] is added and the mixture is stirred at 25°C for 23 h. The solution is diluted with dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel 5 column (60X2.5cm) using 3% increasing to 7% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (1.0719g; 49% yield), FABMS: m/z 249.3 (MH⁺).

Step B:

10 1-N-(Benzylloxycarbonyl)-4-[N-(*tert*-butoxycarbonyl)aminomethyl]piperidine



4-(N-Benzylloxycarbonylaminomethyl)piperidine (0.6814g; 1 equivalent) (prepared as described in Step A above) is dissolved in anhydrous toluene (5 ml) and di-*tert*-butyldicarbonate (0.599g; 1 equivalent) in anhydrous toluene 15 (5 ml) is added dropwise. The mixture is stirred at 0°C for 2h and at 25°C for 20 h. The solution is evaporated to dryness and the residue is taken up in dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is chromatographed on a silica gel 20 column (60X2.5cm) using 0.5% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.9314g; 97% yield), FABMS: m/z 349.3 (MH⁺).

Step C:

25 4-[(*tert*-Butoxycarbonylamino)methyl]piperidine



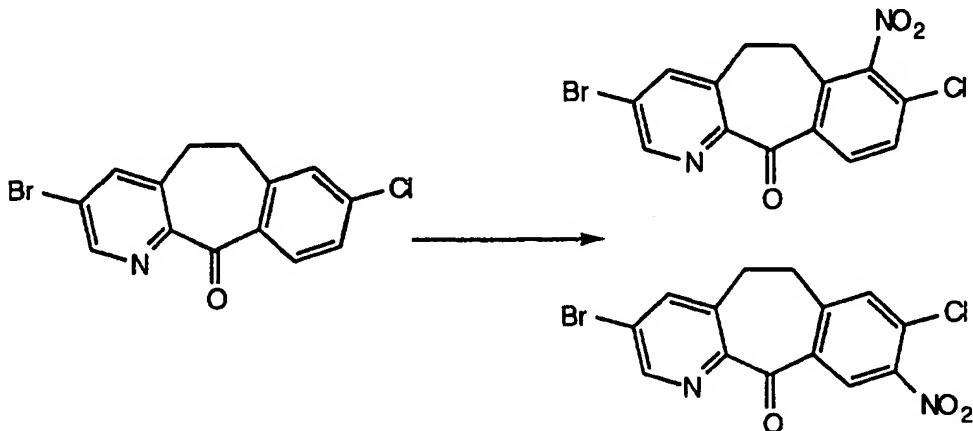
1-N-(Benzylloxycarbonyl)-4-[(*tert*-butoxycarbonylamino)methyl]-piperidine (0.4g) (1 equivalent) (prepared as described in Step B above) is dissolved in methanol (16ml) and 5% Pd-C (0.0638g) is added. The mixture is 30 hydrogenated at 30 psi at 25°C for 17h. The catalyst is removed by filtration through Celite which is washed with methanol. The combined filtrates are evaporated to dryness. The residue is taken up in dichloromethane and washed with 1.0N sodium hydroxide. The dichloromethane layer is dried over magnesium sulfate, filtered and evaporated to dryness. The product is

chromatographed on a silica gel column (45X2.5cm) using 2% increasing to 7% (10% concentrated ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (0.2001g; 81% yield), FABMS: m/z 215.4 (MH⁺).

5

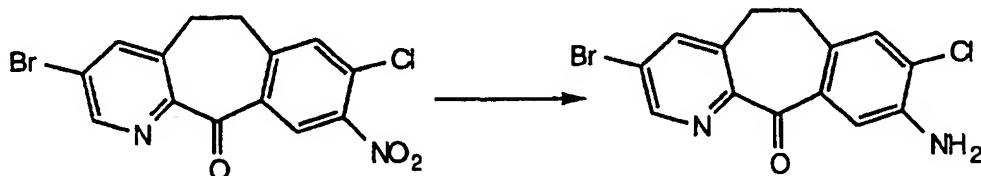
PREPARATIVE EXAMPLE 6

Step A



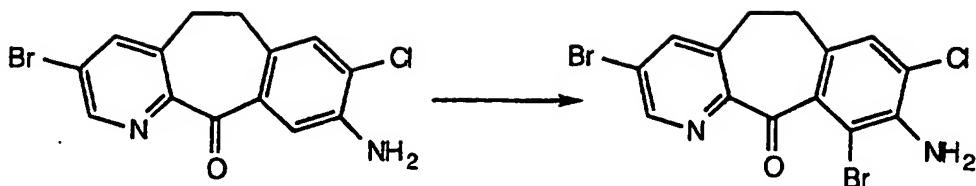
Combine 40.0 g (0.124 mole) of the starting ketone and 200 mL of H₂SO₄ and cool to 0°C. Slowly add 13.78 g (0.136 mole) of KNO₃ over a period of 1.5 hrs., then warm to room temperature and stir overnight. Work up the reaction using substantially the same procedure as described for Preparative Example 4, Step A. Chromatograph (silica gel, 20%, 30%, 40%, 50% EtOAc/hexane, then 100% EtOAc) to give 28 g of the 9-nitro product, along with a smaller quantity of the 7-nitro product and 19 g of a mixture of the 7-nitro and 9-nitro compounds.

Step B



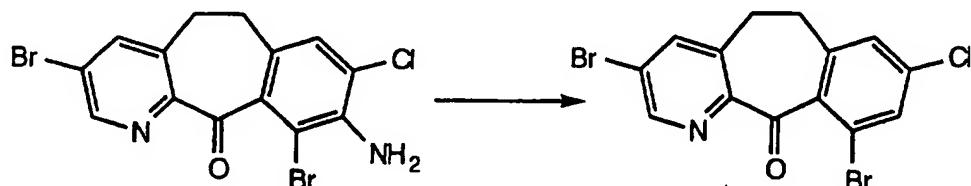
React 28 g (76.2 mmol) of the 9-nitro product of Step A, 400 mL of 85% EtOH/water, 3.8 g (34.3 mmol) of CaCl₂ and 38.28 g (0.685 mole) of Fe using substantially the same procedure as described for Preparative Example 4, Step C, to give 24 g of the product

25 Step C



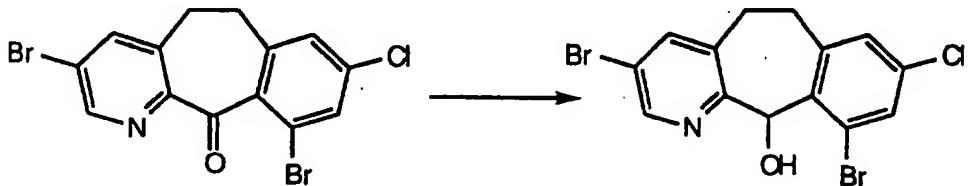
Combine 13 g (38.5 mmol) of the product of Step B, 140 mL of HOAc and slowly add a solution of 2.95 mL (57.8 mmol) of Br_2 in 10 mL of HOAc over a period of 20 min. Stir the reaction mixture at room temperature, then 5 concentrate *in vacuo* to a residue. Add CH_2Cl_2 and water, then adjust to pH = 8-9 with 50% NaOH (aqueous). Wash the organic phase with water, then brine and dry over Na_2SO_4 . Concentrate *in vacuo* to give 11.3 g of the product.

Step D



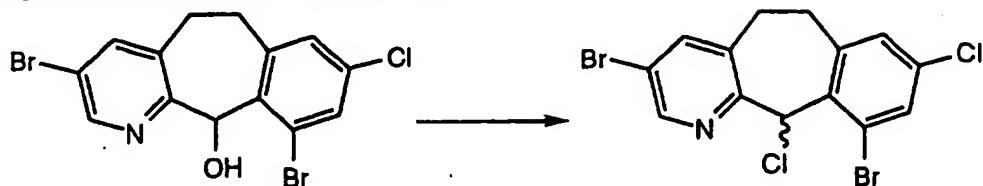
10 Cool 100 mL of concentrated HCl (aqueous) to 0°C, then add 5.61 g (81.4 mmol) of NaNO_2 and stir for 10 min. Slowly add (in portions) 11.3 g (27.1 mmol) of the product of Step C and stir the mixture at 0°-3°C for 2.25 hrs. Slowly add (dropwise) 180 mL of 50% H_3PO_2 (aqueous) and allow the 15 mixture to stand at 0°C overnight. Slowly add (dropwise) 150 mL of 50% NaOH over 30 min., to adjust to pH = 9, then extract with CH_2Cl_2 . Wash the extract with water, then brine and dry over Na_2SO_4 . Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2% EtOAc/ CH_2Cl_2) to give 8.6 g of the product.

20 Step E



25 Combine 8.6 g (21.4 mmol) of the product of Step D and 300 mL of MeOH and cool to 0°-2°C. Add 1.21 g (32.1 mmol) of NaBH_4 and stir the mixture at ~0°C for 1 hr. Add another 0.121 g (3.21 mmol) of NaBH_4 , stir for 2 hr. at 0°C, then let stand overnight at 0°C. Concentrate *in vacuo* to a residue then partition the residue between CH_2Cl_2 and water. Separate the organic phase and concentrate *in vacuo* (50°C) to give 8.2 g of the product.

Step F. 3,10-dibromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine



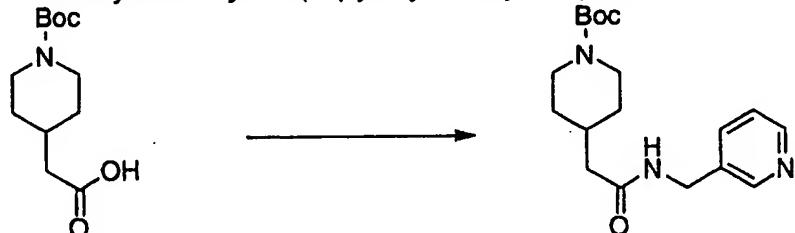
5 Combine 8.2 g (20.3 mmol) of the product of Step E and 160 mL of CH_2Cl_2 , cool to 0°C, then slowly add (dropwise) 14.8 mL (203 mmol) of SOCl_2 over a 30 min. period. Warm the mixture to room temperature and stir for 4.5 hrs., then concentrate *in vacuo* to give the title compound.

PREPARATIVE EXAMPLE 7. N-(3-Pyridylmethyl)-4-piperidineacetamide

10

Step A.

1-*tert*-butoxycarbonyl-N-(3-pyridylmethyl)-4-piperidineacetamide

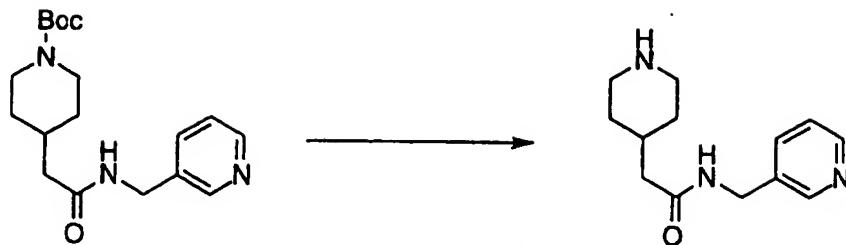


15 1-*tert*-Butoxycarbonyl-4-piperidineacetic acid (5g, 20.55mmoles) (prepared as described in Preparative Example 17, Step A in INO291K), 3-aminomethylpyridine (2.72g, 26.7mmoles), DEC.HCl (5.12g, 26.7mmoles), HOBT (3.61g, 26.7mmoles) and NMM (2.94ml, 26.7mmoles) are dissolved in anhydrous DMF (100ml) and the mixture is stirred under argon at 25°C for 22h. The solution is evaporated to dryness and the residue is dissolved in dichloromethane, washed with 1N NaOH, dried over magnesium sulfate, filtered and evaporated to dryness. The residue is chromatographed on silica gel using 2% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (6.05g, 77%), ESIMS: m/z 334.1 (M^+).

25

Step B.

N-(3-Pyridylmethyl)-4-piperidineacetamide

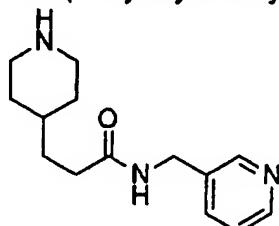


1-*tert*-Butoxycarbonyl-N-(3-pyridylmethyl)-4-piperidineacetamide (5.59g, 16.76mmoles) is dissolved in methanol (100ml) and 10% conc. sulfuric acid in dioxane (v/v) (250ml) is added. The mixture is stirred at 25°C for 2h and the

5 neutralized with Bio Rad AG-1X8 (OH⁻) resin. The resin is washed with methanol and the eluate is evaporated to dryness. The residue is chromatographed on silica gel using 5%-20%-30% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 3.64 g (93% yield) of the title compound: ESIMS: m/z 234.1 (MH⁺).

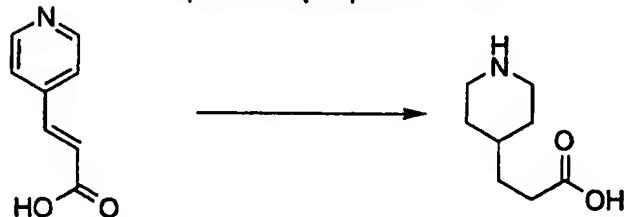
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PREPARATIVE EXAMPLE 8. N-(3-Pyridylmethyl)-4-piperidinepropanamide



Step A.

4-Piperidinepropionic acid



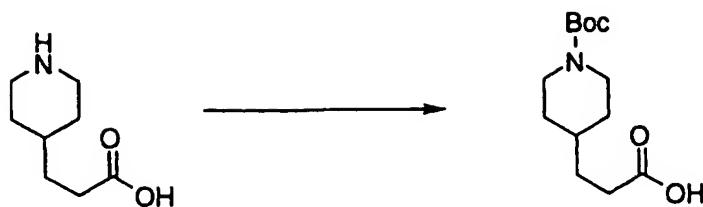
15

3-(4-Pyridyl)acrylic acid (2g, 13.4mmoles) is dissolved in water (70ml) and concentrated hydrochloric acid (1ml). 10% Pd-C (1.5 spatulas) is added and the mixture is hydrogenated at 25°C at 55psi for 72h. The mixture is filtered through Celite® and then passed over a bed of Bio Rad AG 1-X8 (OH⁻) resin.

20 The resin is washed with water and the combined eluates are evaporated to dryness to give the title compound that is used in Step B without further purification.

Step B.

1-*tert*-Butoxycarbonyl-4-piperidinepropionic acid

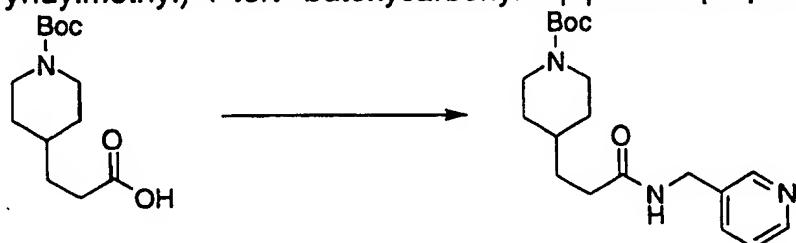


4-Piperidinopropionic acid (13.4mmoles) (prepared as described in Step A above), di-*tert*-butyldicarbonate (3.22g, 14.75mmoles) and sodium hydroxide (0.5364g, 13.4mmoles) are dissolved in THF-water (1:1) (40ml) and the mixture is stirred at 25°C for 18h. The mixture is passed over Bio Rad 50WX4 (H⁺) resin (15ml bed) and the resin is washed with THF-water. The combined eluates are evaporated to dryness and then azeotroped with THF to give the title compound (2.72g, 79%), FABMS: m/z 258.1 (MH⁺).

10

Step C.

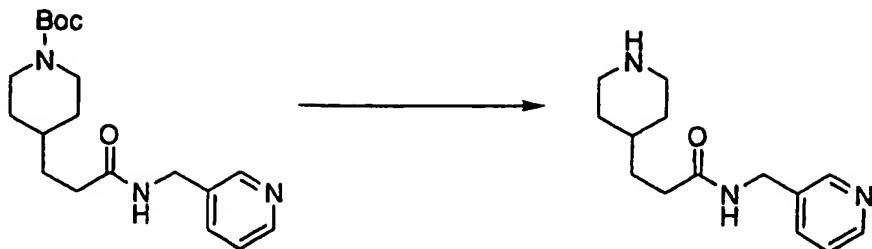
N-(3-Pyridylmethyl)-1-*tert*-butoxycarbonyl-4-piperidinopropanamide



1-*tert*-Butoxycarbonyl-4-piperidinopropionic acid (2g, 7.77mmoles), 3-(aminomethyl)pyridine (1.029ml, 10.1mmoles), DEC.HCl (1.937g, 10.1mmoles), HOBT (1.365g, 10.1mmoles) and NMM (1.111ml, 10.1mmoles) are dissolved in anhydrous DMF (25ml) and the mixture is stirred under argon at 25°C for 20h. The solution is evaporated to dryness and the residue is taken up in dichloromethane, washed with 0.3N NaOH, dried over magnesium sulfate, filtered and evaporated to dryness. The residue is chromatographed on silica gel using 1.5%-2.5% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (2.555g, 95%), ESIMS: m/z 348.1 (MH⁺).

Step D.

25 **N-(3-Pyridylmethyl)-4-piperidinopropanamide**

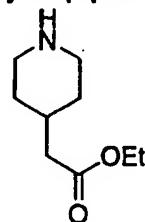


N-(3-Pyridylmethyl)-1-*tert*-butoxycarbonyl-4-piperidinepropanamide (2.222g, 6.4mmoles) is dissolved in methanol (38.15ml) and 10% conc. H₂SO₄ in dioxane (v/v) (95.38ml) is added and the mixture is stirred under argon at

5 25°C for 1.5h. The volume is reduced to half and the mixture is basified to pH 12 with 50% NaOH aq and extracted with dichloromethane. The latter is dried over magnesium sulfate, filtered and evaporated to dryness. The residue is chromatographed on silica gel using 10% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound

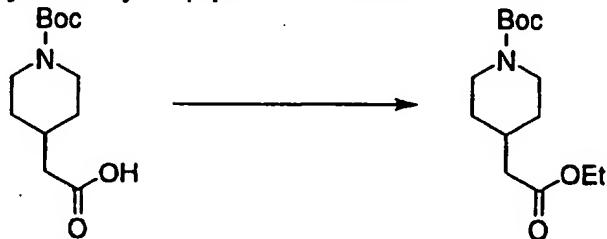
10 (0.9586g, 61%), CIMS: m/z 248.25 (MH⁺).

PREPARATIVE EXAMPLE 9. Ethyl 4-piperidineacetate



Step A.

15 Ethyl 1-*tert*-butoxycarbonyl-4-piperidineacetate



1-*tert*-Butoxycarbonyl-4-piperidineacetic acid (1g, 4.1mmoles) (prepared as described in Preparative Example 17, Step C in INO291K), ethanol (200 proof) (0.284g, 0.362ml, 6.2mmoles), DEC.HCl (1.18g, 6.2mmoles), HOBT (0.8331g, 6.2mmoles) and NMM (0.624g, 0.678ml, 6.2mmoles) are dissolved in anhydrous DMF (30ml) and the mixture is stirred at 25°C under argon for 24h. The solution is evaporated to dryness and the residue is dissolved in dichloromethane, washed with satd, NaHCO₃ aq, water, dried over magnesium sulfate, filtered and evaporated to dryness. The residue is chromatographed on silica gel using 0.5% (10% conc. ammonium hydroxide

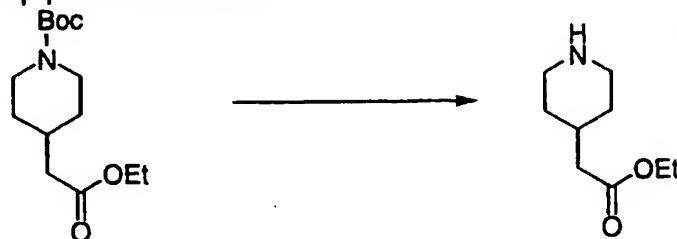
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25

in methanol)-dichloromethane as the eluant to give the title compound (0.682g, 61%), ESIMS: m/z 272.0 (MH⁺).

Step B. Ethyl 4-piperidineacetate

5



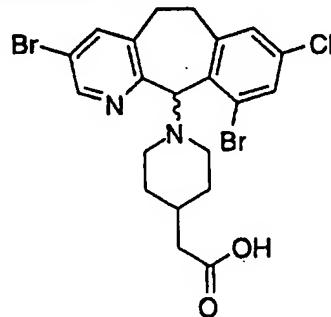
10

Ethyl 1-*tert*-butoxycarbonyl-4-piperidineacetate (0.6g, 2.2mmoles) is dissolved in ethanol (30ml) and 10% conc. H₂SO₄ in dioxane (v/v) (30ml) is added and the mixture is stirred at 25°C for 2h. The mixture is passed over a bed of Bio Rad AG1-X8 (OH⁻) resin and the resin is then eluted with ethanol.

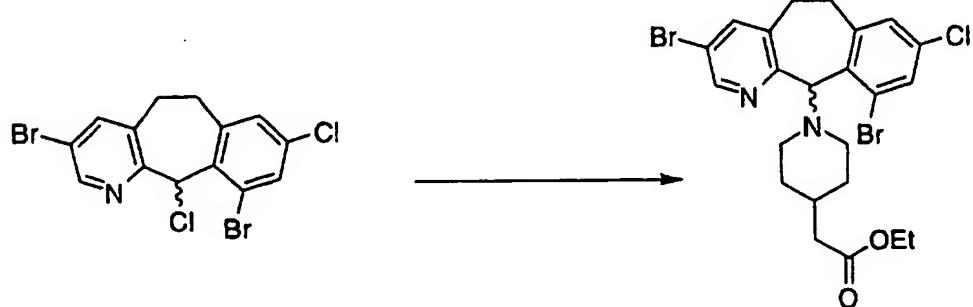
15 The combined eluates are evaporated to dryness and the residue is chromatographed on silica gel using 1% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound.

PREPARATIVE EXAMPLE 10

15 1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetic acid



20 **Step A.**
Ethyl 1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetate



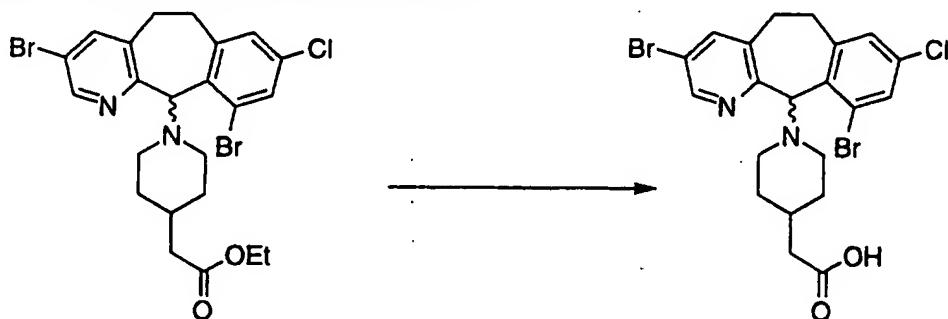
3,10-Dibromo-8,11-dichloro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-b]pyridine (prepared as described in Preparative Example 6, Step F) (0.486g,

1.15mmoles) is dissolved in anhydrous THF (5ml). Ethyl 4-piperidineacetate (prepared as described in Preparative Example 9, Step B) (0.6241g, 2.3mmoles) and triethylamine (0.321ml, 2.3mmoles) in anhydrous THF (5ml) are added and the mixture is stirred at 25°C for 24h. The solution is

5 evaporated to dryness and the residue is dissolved in dichloromethane and washed with 1N NaOH, dried (MgSO₄), filtered and evaporated to dryness. The product is chromatographed on silica gel using 5% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound.

10 Step B.

1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetic acid



15 Ethyl 1-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-4-piperidineacetate (0.3g, 0.5mmoles) (prepared as described in Step A above) is dissolved in ethanol (4ml) and dichloromethane (4ml) and 1M lithium hydroxide in water (1.21mmoles) is added. The mixture is stirred at 50°C for 5h. 1N Hydrochloric acid (1.21mmoles) is added and the solution is evaporated to dryness to give the title compound which is used without further purification.

ASSAYS

20 1. In vitro enzyme assays: FPT IC₅₀ (inhibition of farnesyl protein transferase, in vitro enzyme assay) are determined by the methods disclosed in WO/10515 or WO 95/10516. The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent (IC₅₀ <10 μM) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

30 Under the test protocols employed, there were certain compounds within the scope of the present invention which did not exhibit activity. It is

believed that such compounds would exhibit activity under a different test protocol.

2. Cell-based assay. COS IC₅₀ values refer to the COS cells activity inhibition of Ras processing, are determined by the methods disclosed in WO/10515 or WO 95/10516.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

5 The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated.

10 Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and
15 administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms
20 being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which
25 contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form ExamplesEXAMPLE A-Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
Total		300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen 5 (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B-Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
Total		253	700

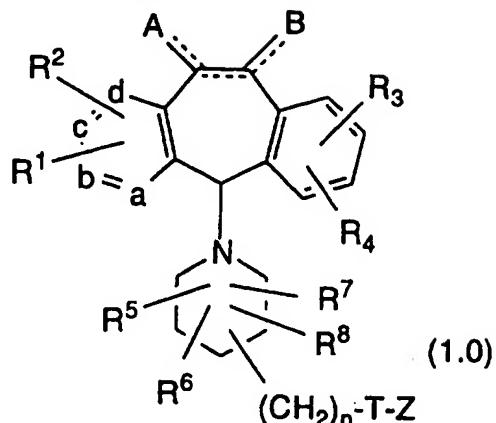
10 Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the 15 specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

5 one of a, b, c and d represents N or NR⁹ wherein R⁹ is O⁻, -CH₃ or -(CH₂)_nCO₂H wherein n is 1 to 3, and the remaining a, b, c and d groups represent CR¹ or CR²; or

10 each of a, b, c, and d are independently selected from CR¹ or CR²;
each R¹ and each R² is independently selected from H, halo, -CF₃, -OR¹⁰,
-COR¹⁰, -SR¹⁰, -S(O)_tR¹¹ (wherein t is 0, 1 or 2), -SCN, -N(R¹⁰)₂, -NR¹⁰R¹¹,
-NO₂, -OC(O)R¹⁰, -CO₂R¹⁰, -OCO₂R¹¹, -CN, -NHC(O)R¹⁰, -NHSO₂R¹⁰,
-CONHR¹⁰, -CONHCH₂CH₂OH, -NR¹⁰COOR¹¹, -SR¹¹C(O)OR¹¹,
-SR¹¹N(R⁷⁵)₂ wherein each R⁷⁵ is independently selected from H and
-C(O)OR¹¹, benzotriazol-1-ylloxy, tetrazol-5-ylthio, or substituted tetrazol-5-
15 ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being
substituted with halo, -OR¹⁰ or -CO₂R¹⁰;

20 R³ and R⁴ are the same or different and each independently
represents H, any of the substituents of R¹ and R², or R³ and R⁴ taken
together represent a saturated or unsaturated C₅-C₇ fused ring to the
benzene ring (Ring III);

25 R⁵, R⁶, R⁷ and R⁸ each independently represents H, -CF₃, -COR¹⁰,
alkyl or aryl, said alkyl or aryl optionally being substituted with -OR¹⁰, -SR¹⁰,
-S(O)_tR¹¹, -NR¹⁰COOR¹¹, -N(R¹⁰)₂, -NO₂, -COR¹⁰, -OCOR¹⁰, -OCO₂R¹¹,
-CO₂R¹⁰, OPO₃R¹⁰, or R⁵ is combined with R⁶ to represent =O or =S and/or
R⁷ is combined with R⁸ to represent =O or =S;

30 R¹⁰ represents H, alkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, aryl,
aralkyl or -NR⁴⁰R⁴² wherein R⁴⁰ and R⁴² independently represent H, aryl,
alkyl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl,
heterocycloalkylalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, alkenyl and
alkynyl;

R¹¹ represents alkyl or aryl;

the dotted line between carbon atoms 5 and 6 represents an optional double bond, such that when a double bond is present, A and B independently represent -NO₂, -R¹⁰, halo, -OR¹¹, -OCO₂R¹¹ or -OC(O)R¹⁰,

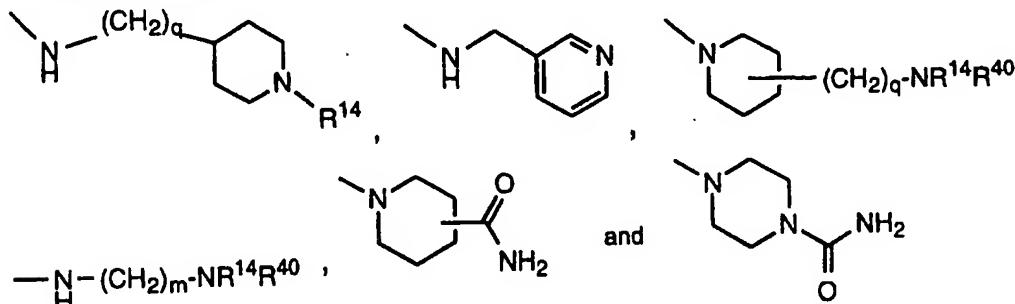
5 and when no double bond is present between carbon atoms 5 and 6, A and B each independently represent H₂, -(OR¹¹)₂, H and halo, dihalo, alkyl and H, (alkyl)₂, -H and -OC(O)R¹⁰, H and -OR¹⁰, oxy, aryl and H, =NOR¹⁰ or -O-(CH₂)_p-O- wherein p is 2, 3 or 4;

n is 0 (zero), 1, 2, 3, 4, 5 or 6;

10 T is -CO-; -SO-; -SO₂-; or -CR³⁰R³¹- wherein R³⁰ and R³¹

independently represent H, alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; and

Z represents alkyl, aryl, aralkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, -OR⁴⁰, -SR⁴⁰, -CR⁴⁰R⁴², -NR⁴⁰R⁴²,

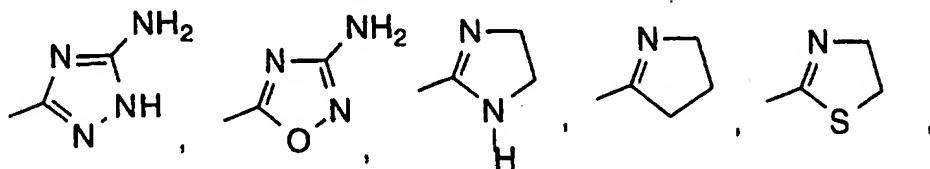


wherein n, R⁴⁰ and R⁴² are defined hereinbefore,

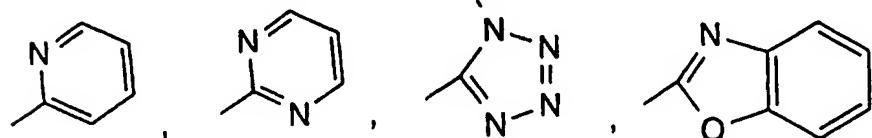
m is 2, 3, 4, 5, 6, 7 or 8;

q is 0 (zero), 1 or 2;

20 and R¹⁴ represents H, C₁₋₆ alkyl, aralkyl, heteroaryl, acyl, carboxamido, carboxamidoalkyl, cyano, alkoxy carbonyl, aralkyloxycarbonyl, D- and L-amino acids covalently bonded through the carboxyl group, imido, imidamido, sulfamoyl, sulfonyl, dialkylphosphinyl, N-glycosyl,



C₆H₅



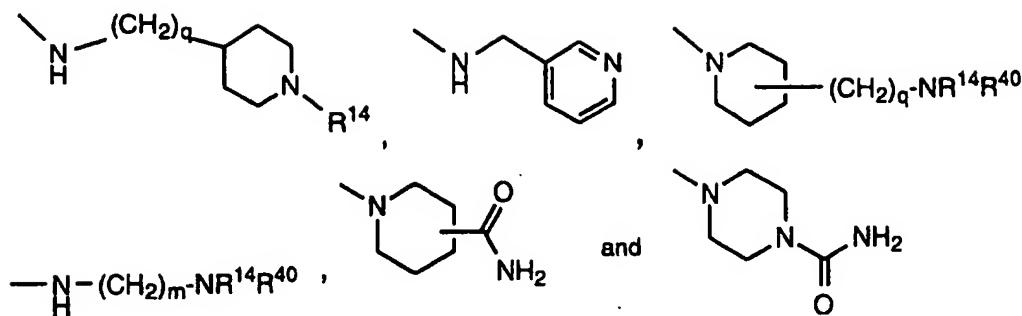
and

25

-C(NHCH₃)=CHNO₂,

with the proviso that when T is -SO-, Z is not -NR⁴⁰R⁴².

2. The compound of claim 1 wherein a is N; b, c and d are carbon;
5 A and B each represent H₂ and the optional double bond is absent.
3. The compound of claim 2 wherein R¹ and R⁴ are H and R² and R³ are halo selected from chloro and bromo; or R¹ is H and R², R³ and R⁴ are halo selected from chloro and bromo.
10
4. The compound of claim 3 wherein R² and R³ are halo in the 3- and the 8-position on the ring structure; or R², R³ and R⁴ are in the 3-, 8- and 10- position on the ring structure.
15
5. The compound of claim 4 wherein R² is Br and R³ is Cl in the 3- and the 8-position on the ring structure; or R² is Br, R³ is Cl and R⁴ is Br in the 3-, 8- and 10- position on the ring structure.
20
6. The compound of claim 5 wherein each of R⁵, R⁶, R⁷ and R⁸ is H.
25
7. The compound of claim 6 wherein the moiety -(CH₂)_n-T-Z is bonded at the 2-, 3- or 4-position on the piperdanyl ring.
30
8. The compound of claim 7 wherein the moiety -(CH₂)_n-T-Z is bonded at the 2- or 3- position on the piperdanyl ring.
35
9. The compound of claim 8 wherein n is zero, 1 or 2; T is -CO- and Z is -NR⁴⁰R⁴² wherein R⁴⁰ and R⁴² independently represent H, aryl, alkyl, aralkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroalkyl, cycloalkyl or cycloalkylalkyl; or
40 Z is



wherein R⁴⁰ is defined hereinbefore,

m is 2, 3 or 4;

5 q is 0 (zero), 1 or 2;

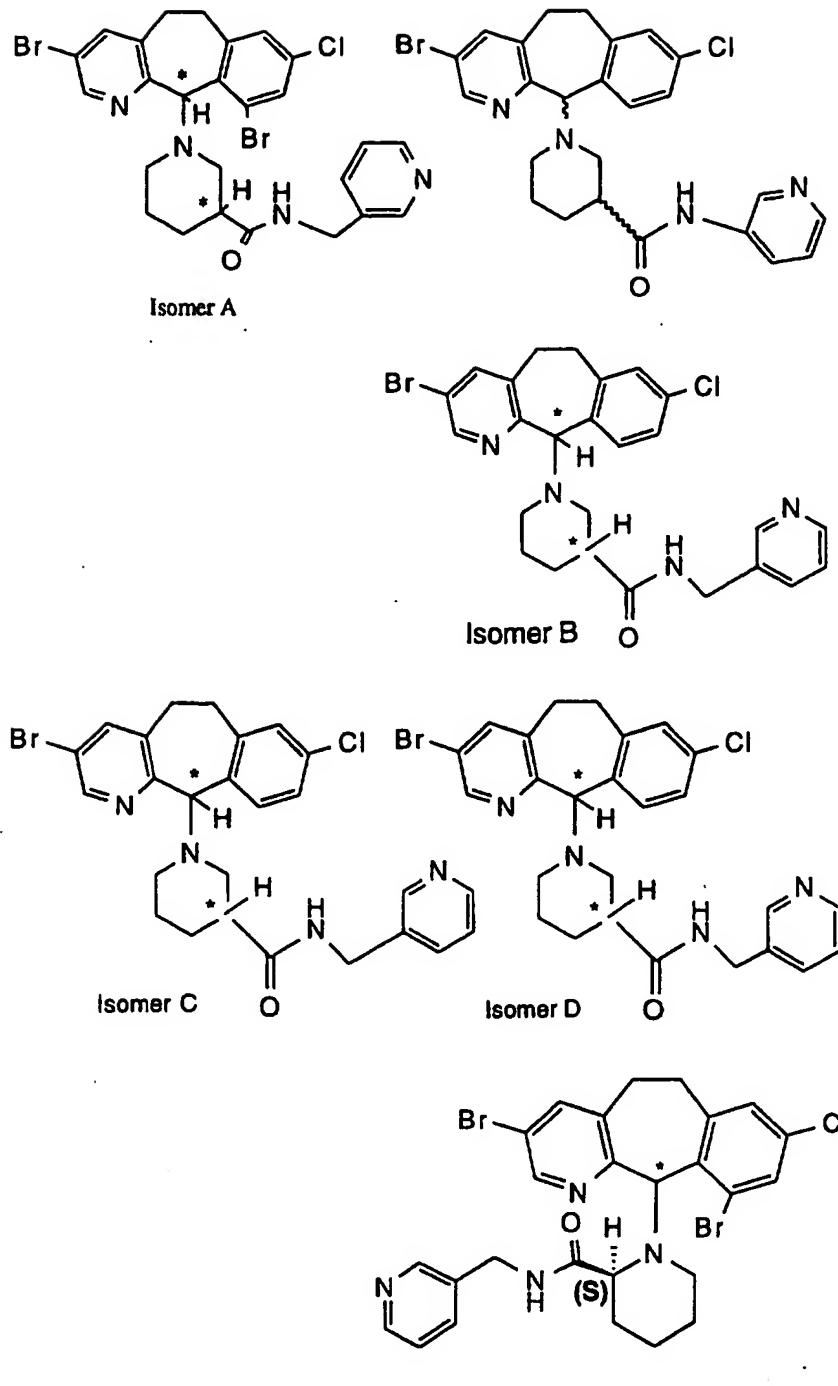
and R¹⁴ represents H, C₁₋₆ alkyl, aralkyl, heteroaryl, acyl, carboxamido, carboxamidoalkyl, cyano, alkoxycarbonyl, aralkyloxycarbonyl imido, imidamido, sulfamoyl, sulfonyl, dialkylphosphinyl, N-glycosyl or C(NHCH₃)=CHNO₂.

10 10. The compound of claim 9 wherein n is zero; Z is -NR⁴⁰R⁴² wherein R⁴⁰ represents H and R⁴² represents heteroarylalkyl.

11. The compound of claim 10 wherein R⁴⁰ is H and R⁴² is 3-pyridylmethyl.

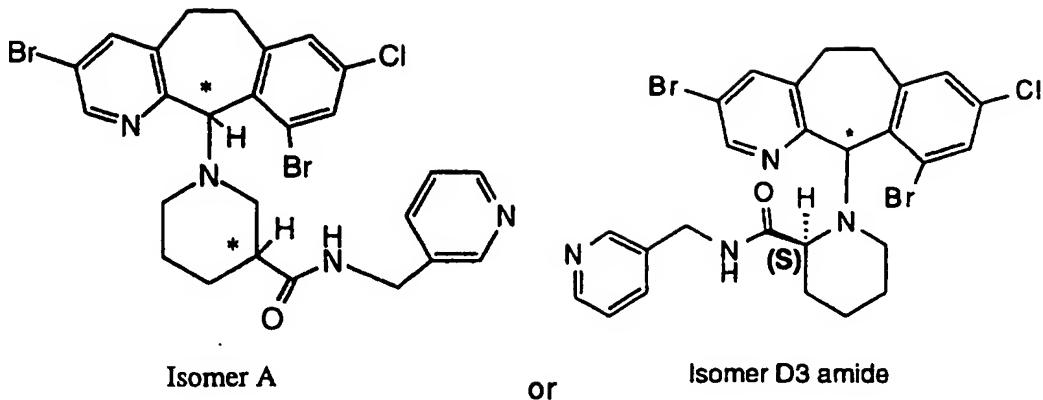
15 12. The compound of claim 9 selected from any of the title compounds of Examples 1-54.

13. The compound of claim 12 which is selected from



or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13 which is



15. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

5

16. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of claim 1.

17. The method of claim 16 wherein the cells inhibited are tumor
10 cells expressing an activated ras oncogene.

18. The method of claim 16 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

19. The method of claim 16 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of ras farnesyl protein transferase.

20. The method of claim 16 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 97/15903

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/14 C07F9/6558 C07H19/04 C07D401/04 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 396 083 A (SCHERING CORP) 7 November 1990 see claims ---	1,15-20
A	WO 92 00293 A (SCHERING CORP) 9 January 1992 see claims ---	1,15-20
A	WO 95 10515 A (SCHERING CORP) 20 April 1995 see claims ---	1,15-20
A	WO 95 10516 A (SCHERING CORP) 20 April 1995 see claims ---	1,15-20
		-/-



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search

24 November 1997

Date of mailing of the international search report

02.12.97

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Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/US 97/15903

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 593 417 A (SQUIBB & SONS INC) 15 July 1981 see page 20, line 15 - page 22, line 4; claims; examples 73-94 -----	1,15-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/15903

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Remark : Although claims 16-20 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. Application No

PCT/US 97/15903

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Information on patent family members

Internat'l Application No

PCT/US 97/15903

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